CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215039Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	215039
Priority or Standard	Priority
Submit Date(s)	10-06-2021
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PDUFA Goal Date	04-06-2022
Division/Office	Division of Oncology 2 (DO2)/Office of Oncologic Diseases (OOD)
Review Completion Date	04-05-2022
Established Name	Alpelisib
(Proposed) Trade Name	Vijoice
Pharmacologic Class	Kinase inhibitor
Code name	BYL719
Applicant	Novartis
Formulation(s)	Tablets
Dosing Regimen	50 mg orally once daily for patients aged 2 to 17 years old 250 mg orally once daily for adult patients
Applicant Proposed Indication(s)/Population(s)	Treatment of adult and pediatric patients aged 2 years and older with PIK3CA-Related Overgrowth Spectrum (PROS)
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
ATU	Temporary Authorization for Use
BMI	Body mass index
BNP	B-type natriuretic peptide
BSEP	Bile salt export pump
CLAPO	Capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry with partial/generalized overgrowth
CLOVES	Congenital lipomatosis with overgrowth, vascular malformations, epidermal nevi, and skeletal/scoliosis/spinal abnormalities
CRO	Contract research organization
CRS	Case retrieval strategy
CT	Computerized tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DI	Dose intensity
DMP	Data management plan
DOR	Duration of response
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
ER	Emergency room
FAO	Fibroadipose overgrowth
FIL	Facial infiltrating lipomatosis
FLACC	Face, legs, activity, cry consolability
GI	Gastro intestinal
HHML	Hemihyperplasia multiple lipomatosis
HR	Hormone receptor
HRU	Healthcare resource use

ICRR	Independent central radiology review
KTS	Klippel-Trenaunay syndrome
LON	Lipomatosis of nerve
MAP	Managed Access Program
MATE1	Multidrug and toxin extrusion-1
MCAP	Megalencephaly–capillary malformation polymicrogyria
MRI	Magnetic resonance imaging
MRP2	Multidrug resistance-associated protein 2
PD	Progressive disease
PDI	Planned dose intensity
PROS	PIK3CA-related overgrowth spectrum
PT	Preferred term
RDI	Relative dose intensity
SAE	Serious adverse event
SD	Standard deviation
SDS	Standard Deviation Scores
SOC	System organ class
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Alpelisib (BYL719) is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. On May 24, 2019, the FDA approved NDA 212526 for alpelisib tablets (trade name: PIQRAY) in combination with fulvestrant for the treatment of postmenopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated advanced or metastatic breast cancer. On October 6, 2021, Novartis submitted NDA 215039, a Type 10 NDA, under Section 505(b)(1) of the Food, Drug, and Cosmetic Act. The Applicant proposed the following indication for alpelisib (VIJOICE):

> *For the treatment of adult and pediatric patients aged 2 years and older with PIK3CA-Related Overgrowth Spectrum (PROS)*

The recommended dosage for the proposed indication is 50 mg to 250 mg once daily based on age.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The FDA review teams for all disciplines agree that the submitted evidence meets the statutory evidentiary standard for accelerated approval as described in 21 CFR part 314.510 Subpart H. The review teams recommend that accelerated approval be granted for alpelisib for the following indication:

> *For the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy.*

The recommendation for accelerated approval is based on the results from a single-arm clinical study in patients who were treated as part of an expanded access program for compassionate use, EPIK-P1 (NCT04285723). Eligible patients 2 years of age or older who received alpelisib had clinical manifestations of PROS that were assessed by the treating physician as severe or life-threatening and necessitating systemic treatment and had documented evidence of mutation in the PIK3CA gene as determined by a local laboratory. Patients received alpelisib at dosages based on age ranging from 50 mg to 250 mg orally once daily.

In EPIK-P1, the primary endpoint was response (yes/no) at Week 24 or 6 months (+/- 4 weeks) by the blinded independent central review (BIRC). A response was defined by achieving at least

20% reduction from the index date in the sum of measurable target lesion volume (1 to 3 lesions), by MRI or CT-scan, provided that none of the individual target lesions had at least ≥ 20% increase from the index date to Week 24 or 6 months (+/- 4 weeks) and in the absence of progression of non-target lesions and without new lesions. Patients who permanently discontinued alpelisib prior to 24 weeks of treatment, patients who required surgery as rescue therapy between the index date and 24 weeks of treatment and patients with MRI scan performed at Week 24 or 6 months (+/- 4 weeks) for which the volumetric measurement of the selected target lesions was not calculated (i.e. unknown) were defined as non-responders. The confirmed response rate in the 37 patients comprising the efficacy population was 27% (95% CI: 14, 44). The median duration of response (DOR) was not reached (range: 0.9+, 42.9+ months), and 60% of patients had a duration of response lasting at least 12 months.

Since PROS lesions would not be expected to regress in the absence of active therapy, the review team considered the endpoint of radiologic response rate at Week 24 as reasonably likely to predict clinical benefit. In particular given the nature of PROS as impacting mobility and function it is reasonably likely to expect a decrease in tumor size to result in clinical benefit. Given the highly persuasive magnitude of the observed response rate, an endpoint reasonably likely to predict clinical benefit, with supportive duration of response, and taking into account the rarity of the condition and lack of alternative treatments, the review team considered the results to provide substantial evidence of the effectiveness of alpelisib and to be supportive of accelerated approval.

In order to obtain the information needed to verify the clinical benefit of alpelisib, the Applicant has agreed to a postmarketing requirement (PMR) that will provide the additional data needed to verify clinical benefit. To fulfill the PMR, the Applicant plans to submit data from the ongoing EPIK-P2 trial, a randomized (2:1) clinical trial with an initial double-blind placebo-controlled period with crossover at 16 weeks. Response rate data will be obtained to provide additional precision around the point estimate of response by various PIK3CA mutation types and age ranges. Clinical outcome assessment data will be systematically collected to confirm that volumetric reduction in PROS lesions provides a clinical benefit to patients. Duration of response will be followed out to 3 years to confirm response rate and benefit are maintained. Additionally, the study required under the PMR will enroll patients across a large number of clinical sites internationally in order to ensure that alpelisib is studied in an appropriately diverse patient population with respect to race, ethnicity, mutation type, PROS subtype, and age.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

PIK3CA-Related Overgrowth Spectrum (PROS) is an umbrella term for a group of rare overgrowth disorders that results from somatic gain-of-function alterations in the PIK3CA gene, activating the phosphatidylinositol/AKT/mTOR pathway (Keppler-Noreuil et al., 2015) . These clinical entities are heterogeneous in both genotype and phenotype but are generally characterized by asymmetric and sporadic lesions that can result in progressive disability (Mirzaa et al., 2013). Although the prevalence of PROS is difficult to estimate due to its rarity, recent characterization and potential misdiagnosis, based on data compiled by the Applicant from NIH Genetics Home Reference and Orphanet, it is estimated to affect approximately 14 per million patients (i.e., less than 5, 000 patients in the United States). Patients have few options for treatment of their disease, which include surgery (debulking or amputation, which are associated with high risk of regrowth), sclerotherapy, endovascular occlusive procedures, off-label use of sirolimus and symptomatic treatment. There are currently no FDA-approved therapies for PROS.

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα that has previously been approved, under the trade name PIQRAY, in combination with fulvestrant for the treatment of post-menopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated advanced or metastatic breast cancer.

The effectiveness of alpelisib for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS who require systemic therapy was established based on data from 37 patients in study EPIK-P1, a single-arm clinical study in patients who were treated as part of an expanded access program for compassionate use. Eligible patients had clinical manifestations of PROS that were assessed by the treating physician as severe or life-threatening and necessitating systemic treatment and had documented evidence of mutation in the PIK3CA gene as determined by a local laboratory. Patients received alpelisib at dosages based on age ranging from 50 mg to 250 mg orally once daily. The major efficacy outcome measure for the study was the proportion of patients with radiological response at Week 24 as determined by blinded independent central radiology review (BICR), defined as a ≥ 20% reduction from baseline in the sum of measurable target lesion volume (1 to 3 lesions) and confirmed by at least one subsequent imaging assessment. The confirmed response rate was 27% (95% CI: 14, 44). The majority (60%) of responders exhibited a response lasting at least 12 months, including some patients (30%) with a documented response of 24 months' or greater duration. All patients who demonstrated a radiologic response had the Congenital Lipomatous Overgrowth Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal (CLOVES) subtype of PROS and a PIK3CA mutation that was reported in ≥2% of

PROS cases and categorized as "frequent" by the Applicant.

The safety of alpelisib was assessed in 57 patients 2 years of age and older with severe or life-threatening PROS who received alpelisib at age-based dosages ranging from 50 mg to 250 mg orally once daily. Among patients who received alpelisib, 95% were exposed for 6 months or longer and 79% were exposed for greater than one year.

Based on experience in the oncology population, alpelisib can cause severe toxicities including severe hypersensitivity, severe cutaneous adverse reactions, hyperglycemia, pneumonitis, and diarrhea. Not all toxicities observed with alpelisib in the oncology setting (i.e., those included in the PIQRAY label) were directly observed in the safety population in EPIK-P1. However, given the small size of the safety database in this study, the lack of observation of these severe adverse events does not represent strong evidence that these events will not occur in patients with PROS. Therefore, the product label for VIJOICE includes all Warnings and Precautions included in the PIQRAY label, including severe hypersensitivity, severe cutaneous adverse reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity.

The most common adverse reactions (≥ 10%) were diarrhea, stomatitis, and hyperglycemia. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were increased glucose, decreased hemoglobin, decreased phosphate, increased bilirubin, decreased sodium and decreased platelets. The safety population included patients 2 – 50 years of age. Analyses of safety by subgroup based on age were limited by small numbers of patients, but there were no new safety signals identified in pediatric patients (n=39) based on the results of EPIK-P1. Given the growth plate and tooth abnormalities observed in nonclinical studies, and the lack of dedicated, prospective monitoring of growth and development in the children enrolled in EPIK-P1, there is a post-marketing requirement to provide long-term prospective data to better assess specific safety issues with alpelisib in children.

Given the rarity of PROS and the lack of an approved or standard systemic treatment, the FDA considered data from EPIK-P1 appropriate for evaluation of efficacy in this population. The review team considers that the confirmed response rate in EPIK-P1, along with the observed duration of responses as reasonably likely to predict clinical benefit and sufficient to support accelerated approval of alpelisib in patients with severe manifestations of PROS. Data from additional patients in this patient population including a further description of duration of response out to 36 months, in addition to prospectively collected information to further evaluate patient outcomes, are needed to confirm the clinical benefit of alpelisib in patients with severe manifestations of PROS. The risks associated with alpelisib appear acceptable for in the rare population of patients with severe manifestations of PROS, who have a high unmet medical need and previously had no approved therapies for their disease. The product label informs providers of potential risks associated with alpelisib and provides adequate instructions to mitigate

these risks to ensure its safe and effective use in the indicated patient population.

In the opinion of the FDA review team, alpelisib has a favorable benefit-risk profile for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• PROS (PIK3CA-related overgrowth spectrum) is an umbrella term for a group of rare overgrowth disorders that results from somatic gain-of-function alterations in the PIK3CA gene, activating the phosphatidylinositol/AKT/mTOR pathway. These clinical entities are heterogeneous in both genotype and phenotype but are generally characterized by asymmetric and sporadic lesions that can result in progressive disability. Although the prevalence of PROS is difficult to estimate due to its rarity, recent characterization and potential misdiagnosis, it is estimated to affect approximately 14 per million patients (i.e., less than 5, 000 patients in the United States). • The diagnostic criteria for PROS include presence of a somatic PIK3CA mutation, congenital or early childhood onset, and patchy or irregular overgrowth (Keppler-Noreuil et al., 2015). Patients may manifest either a spectrum of disease features with at least two of the following: segmental overgrowth, vascular malformation, and epidermal nevus, or they may present with isolated features such as lymphatic malformation or macrodactyly. Tissues in the affected overgrowth can include all or some of these types: fibrous, adipose, vascular, nervous and skeletal. • Specific PROS diagnostic subtypes include Fibroadipose hyperplasia or Overgrowth (FAO); Hemihyperplasia Multiple Lipomatosis	PROS is a serious and potentially life threatening disease with a high unmet medical need. Spontaneous regression of these lesions has not been reported thus examination of PROS in the setting of historical lack of spontaneous regression is appropriate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(HHML); Congenital Lipomatous Overgrowth Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal (CLOVES) syndrome; Fibroadipose Infiltrating Lipomatosis (FIL), and Megalencephaly-Capillary Malformation (MCAP); and Klippel-Trenaunay syndrome (KTS) (Keuntz et al., 2017). • PROS lesions are not considered cancerous. Although growth trajectories of these lesions can vary, based on descriptions of PROS in the medical literature, most patients have a progressive course. Further, spontaneous regression of these lesions has not been reported. • The severity of PROS is highly variable, ranging from mild, localized disease to severe, extensive, debilitating, and potentially life-threatening disease manifesting as overgrowths that adversely impact major vessels or critical organs. Accordingly, PROS can result in a range of clinical complications. These morbidities are typically dependent on the size and anatomical location of the lesion and can include organ dysfunction, functional impairment, mobility issues, pain, thromboembolism, hemorrhage, and infection. • It is hypothesized that the phenotypic diversity of segmental overgrowths and their overlapping features may be due to the timing of the mutation's occurrence during or after embryonic development, tissue localization of the mutation, the level of mosaicism present and potential allelic heterogeneity (Akgumus et al., 2017).	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are no FDA-approved drugs for the treatment of PROS. • Management options primarily consist of surgical debulking or amputation (although there is a high risk of regrowth), sclerotherapy, endovascular occlusive procedures, off-label use of the mTOR inhibitor sirolimus (considered on a case-by-case basis), symptom and pain treatment, and other interventions such as physical therapy (Mirzaa et al., 2013).	There are no FDA-approved treatment options. Safe and effective treatments for this highly morbid condition are needed.
Benefit	• The results from EPIK-P1 demonstrate a confirmed response rate of 27% (95% CI: 14, 44) per criteria based on volumetric reduction of target lesions as assessed by blinded independent central review (BICR), as well as durable responses. The majority (60%) of responders exhibited a response lasting at least 12 months, including some patients (30%) with a response of 24 months' or greater duration. • Given the small numbers of patients overall and particularly within subgroups defined based on PROS subtype and specific PIK3CA mutation, and the phenotypic and genotypic heterogeneity of the patient population, there is residual uncertainty regarding the consistency of treatment effect of alpelisib across the population of patients with PROS. • The majority of patients (77%) in EPIK-P1 were enrolled from a single site in France, though the study included sites in other countries including the US. The treatment landscape for PROS is consistent between France and the US, and there are no known differences in disease biology or epidemiology between these countries.	Substantial evidence of effectiveness supporting accelerated approval was demonstrated for alpelisib in the indicated patient population based on results of EPIK-P1. All patients in EPIK-P1 with radiologic responses had the CLOVES subtype of PROS and had PIK3CA mutations categorized as frequent, but shrinkage in the size of volumetric lesions not meeting the pre-defined threshold for response was also observed in patients with non-CLOVES subtypes. PROS is a heterogeneous disease with respect to mutation type and phenotype, and EPIK-P1 had a limited sample size. In order to verify and further characterize the clinical benefit for this population an

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		understanding of long-term DOR and confirmation of clinical benefit based on clinical outcomes are needed. A post-marketing requirement (PMR) will be issued to collect additional data from a sufficient number of patients with severe manifestations of PROS in a multiregional clinical trial. Patients with a radiologic response will be followed for at least 36 months from the onset of response or until disease progression. An evaluation of responses amongst relevant subgroups (i.e., based on PIK3CA mutation type, PROS subtype, and age) will be requested in the PMR to further evaluate the consistency and reproducibility of the treatment effect with alpelisib. In order to further support generalizability to the US population, the distribution of race and ethnicity in the patient population studied in the trial should be sufficiently reflective of the epidemiology of the disease to support generalizability of results to U.S. patients with PROS. A post-marketing commitment will be also issued to assess whether further dose optimization is needed in pediatric patients by assessing a higher starting dose (125 mg) in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		patients 6 to 17 years of age.
Risk and Risk Management	• Fifty-seven patients 2 years of age and older with severe or life-threatening PROS received alpelisib based on age at dosages ranging from 50 mg to 250 mg orally once daily. Among patients who received alpelisib, 95% were exposed for 6 months or longer and 79% were exposed for greater than one year. • The most common adverse reactions (≥ 10%) were diarrhea, stomatitis, and hyperglycemia. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were increased glucose, decreased hemoglobin, decreased phosphate, increased magnesium, decreased magnesium, and decreased neutrophil and decreased lymphocyte count. • Not all toxicities observed with alpelisib in the oncology setting (i.e., those included in the PIQRAY label) were directly observed in the safety population in EPIK-P1. However, given the small size of the safety database, the lack of observation of these severe adverse events does not provide strong evidence that these events will not occur in patients with PROS. Therefore, the product label includes all Warnings and Precautions included in the PIQRAY label, including severe hypersensitivity, severe cutaneous adverse reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity. • Analyses of safety by subgroup based on age were limited by small numbers of patients, but there were no new safety signals identified	While alpelisib can cause severe toxicities, these toxicities are generally manageable and safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations in product labeling. The observed safety profile of alpelisib is acceptable when assessed in the context of the treatment of a potentially life-threatening disease. The review team did not consider that a Risk Evaluation and Mitigation Strategy (REMS) was warranted to ensure the safe use of the product given the information included in the product label. Postmarketing requirements will be issued for data from clinical trials to fulfill the requirement of accelerated approval, to provide additional data to characterize the serious risks of alpelisib in patients with PROS, and to further characterize the safety in pediatric and adolescent patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in pediatric patients based on the results of EPIK-P1.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			Section 8.1.2, Study Results: Efficacy Results- Secondary or exploratory COA (PRO) endpoints
			□	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			

	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Diana Bradford, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:
Somatic activating mutations in the PIK3CA gene have been found to induce a spectrum of clinically recognizable overgrowth and malformation disorders now commonly known as PROS (De Santis et al 2017). Somatic mutations occur during the post fertilization/zygotic phase of embryogenesis with most affected patients presenting with a pathogenic variant of PIK3CA. The mutations in PIK3CA gene (coding for catalytic subunit, p110α, of the protein PI3K) lead to a hyperactivation of the PI3K/AKT/mTOR pathway and to the development of heterogeneous mosaic segmental overgrowth disorders.

PROS is considered as a group of rare diseases with diverse phenotypes, including (but not limited to): fibroadipose hyperplasia or overgrowth (FAO), hemihyperplasia multiple lipomatosis (HHML), congenital lipomatosis with overgrowth, vascular malformations, epidermal nevi, and skeletal/scoliosis/spinal abnormalities (CLOVES) syndrome, macrodactyly, fibroadipose infiltrating lipomatosis/facial infiltrative lipomatosis, megalencephaly–capillary malformation polymicrogyria (MCAP), dysplastic megalencephaly, capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry with partial/generalized overgrowth (CLAPO), lipomatosis of nerve (LON),and Klippel-Trenaunay syndrome (KTS) (Keppler-Noreuil 2015) (Hughes M, Hao M, Luu M 2020).

The prevalence of PROS is difficult to estimate because of its rarity, its recent characterization (Keppler-Noreuil et al 2014), variation in ascertainment, the broad phenotypic spectrum, and the occurrence of atypical or mild phenotypes leading to misdiagnosis (Keppler-Noreuil et al 2014; Mirzaa et al 2013). Novartis compiled data from NIH Genetics Home Reference and Orphanet to assess the prevalence. The estimated prevalence of the following five combined PROS conditions is about 14 per 1,000,000: MCAP syndrome, hemihyperplasia multiple lipomatosis, macrodactyly, fibroadipose hyperplasia, and KTS. Based on the most current US population estimate of 332,582,420 (US Census Bureau, August 2021), the summation results in less than 4,700 patients with PROS in the United States.

The clinical characteristics of PROS can be diverse and depend on the timing of the mutation during embryogenesis and the organs affected. PROS is characterized by congenital or early childhood-onset overgrowth, sporadic occurrence, and mosaic distribution. Segmental overgrowth is often congenital in onset, but it is usually noted by one year of age with progressive overgrowth of tissues persisting in some cases into adulthood (Keppler-Noreuil et al 2016). PIK3CA-related overgrowth syndromes are clinically recognizable conditions and are

associated with cutaneous, vascular, musculoskeletal, and/or cerebral abnormalities, as well as focal or segmental overgrowth of the body. Due to the extensiveness of vascular malformations and tissue overgrowth, PIK3CA-related syndromes pose a therapeutic challenge.

The severity of PROS is highly variable, ranging from localized overgrowth to severe, extensive, and life-threatening overgrowth affecting major vessels and/or critical organs (Madsen et al 2018). PROS may be conceived of as a highly anatomically variable mixture of overgrown tissues, with vasculature (capillaries, veins and lymphatics) and adipose tissues often most dramatically affected macroscopically. Many other tissues and organs, including bone, brain, peripheral nerves, liver, skeletal and cardiac muscle can also be affected.

Functional impairment (e.g., of walking or swallowing), renal impairment, cardiac impairment, pain, recurrent superficial infections, impaired neurological development, seizures, thromboembolisms, pulmonary hypertension, and hemorrhages, amongst other manifestations can be a consequence of the overgrowth; all of which may be debilitating and may cause early mortality.

The responsible activated PI3K/AKT/mTOR signaling pathway and the progressive nature of this disorder makes it a good target for pharmaceutical therapy since downregulation of the pathway may prevent progression that is seen in many patients (Keppler-Noreuil K et al, 2014).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of PROS and has the following additional comments. PROS is an umbrella term for several clinical entities resulting from *PIK3CA*-activating mutations and are heterogenous in genotype and phenotype, presenting with diverse manifestations that vary in severity. The wide spectrum of overgrowths and vascular malformations and their distribution may be explained by the timing of the inciting mutation's occurrence during embryonic development, tissue localization of the mutation, level of mosaicism and potential allelic heterogeneity. Although PROS is typically progressive during childhood, some patients may continue to experience progressive overgrowth into adulthood. Despite the phenotypic variability observed, review of the medical literature and the natural history of PROS does not appear to support spontaneous regression of these lesions.

2.2. Analysis of Current Treatment Options

There is currently no cure for any of the disorders classified under the PROS umbrella nor any approved pharmacological treatment for this disease. As such, current treatment relies on supportive care which is comprised of surgical debulking, amputations, orthopedic procedures to limit growth, and blocking of overgrowth vessels (sclerotherapy, endovascular occlusive procedure). Patients may experience recurrence following surgery, and repeat surgeries are frequently required. In one study of 35 patients (median age, 7 years), 83% had undergone surgery, with more than half requiring multiple surgeries (Keppler-Noreuil et al 2014). In addition, supportive care is often necessary and may include symptom and pain management, nutritional support, psychological support (Venot et al 2018, Engel-Nitz NM et al 2021).

The Applicant's Position:
Patients with PROS have a significant unmet medical need for new and more effective therapeutic approaches, including pharmacological treatments. Future targeted therapies may be possible with the identification of activated PI3K/AKT signaling, either through inhibition of PI3K, or AKT, or of downstream pathways such as mTOR.

Table 1: Summary of Treatment Armamentarium Relevant to PROS

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
There is currently no FDA approved treatment for PROS						
Non-approved Treatments						
Sirolimus[(1)]	PROS	Not applicable	Adults: 1.2 mg once daily in capsules Children: 0.58 mg twice daily in oral solution	Modestly reduced overgrowth in patients 3 to 65 years of age with PROS	The side-effect profile is significant, mandating individual risk-benefit evaluation for sirolimus treatment in PROS	None
Source: [(1)] Parker et al 2019.						

In addition to alpelisib, Sirolimus is under clinical investigation for PROS in as summarized above in Table 1.

The FDA's Assessment:
The FDA agrees with the Applicant's discussion of current treatment options for patients with PROS and notes that sirolimus has been used off-label in patients with PROS. The PROMISE trial (NCT02428296) was a nonrandomized, open label, investigator-initiated study of low-dose sirolimus in 39 patients (aged 3 to 48 years) with a diagnosis of PROS with progressive overgrowth and a mosaic *PIK3CA* variant (Parker et al., 2019). The primary outcome was percentage change in the tissue volumes of affected and unaffected sites as measured by dual energy X-ray absorptiometry [DXA] during 26 weeks of untreated run-in followed by 26 weeks of sirolimus administration. The investigators reported a reduction of 7.2% (standard deviation [SD] 16.0; p=0.04) in the volume of affected tissues during sirolimus treatment. No differences were detected in quality of life scores before and after sirolimus treatment among children or adults. Study findings were notable for 28 (72%) of 39 patients having at least one adverse event (AE) possibly related to sirolimus. There were 21 serious adverse events occurring among 12 patients during the run-in or treatment period, and 7 patients had AEs leading to sirolimus discontinuation. As noted by the study investigators, based upon these results, use of sirolimus may be considered on a case-by-case basis.

Another study by Adams et al. (2016) assessed a higher dose of sirolimus in a heterogenous cohort of patients with primarily vascular malformations. Although genetic characterization was not reported, some patients were likely to have PROS based on clinical phenotypes. Sirolimus was administered in 28-day courses. Sixty-one patients were enrolled, with 57 patients evaluable for efficacy at the end of 6 courses, and 53 evaluable at the end of 12 courses. Disease response was determined by radiologic assessment, a functional impairment score and health-related quality of life (QOL). No patient exhibited a complete response, and 87% of participants had a partial response, and in some cases only due to changes in QOL measures. Grade 3 and higher toxicities attributed to sirolimus included blood and bone marrow-related AEs in 27% of patients. Two patients were unable to complete treatment due to drug-related toxicity.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Alpelisib in combination with fulvestrant was approved by the US Food and Drug Administration (FDA) on 24-May-2019 under the name of Piqray® for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
The alpelisib in PROS clinical development program was designed in consultation with Health Authorities from different regions, including the US and the EU. Key meetings with FDA are listed in Table 2.

Alpelisib was granted breakthrough therapy designation by the FDA for the treatment of PROS on 13-Nov-2019. Novartis received orphan drug designation for alpelisib for the treatment of PROS by the FDA (DRU-2019-7108) on 18-Nov-2019 and by the EMA (EU/3/21/2420) on 26-Mar-2021.

Table 2: Key Health Authority Interactions

Health Authority - interaction type	Meeting date	Comments
US FDA – pre-IND meeting	25-Jul-2019	FDA supported the proposed development plan and confirmed that data derived from EPIK-P1 could serve as the basis for an application to seek approval.
US FDA – Type B meeting	02-Apr-2020	FDA agreed to the content of the NDA and that Novartis can submit a separate, Type 10 NDA in support of the PROS indication under a distinct proprietary name and with a distinct label. FDA agreed that the NDA would be exempt from the Pediatric Research Equity Act (PREA) requirements and not subject to the amended FDA Reauthorization Act (FDARA) regulations. FDA also agreed to review the NDA under the Real Time Oncology Review (RTOR) Program and to waive the requirement for the 120-day Safety Update.
US FDA email communication regarding the EPIK-P1 sample size and site selection	06-Oct-2020	FDA noted that they do not have concerns regarding the anticipated EPIK-P1 sample size and that they do not have any questions or comments regarding EPIK-P1 site selection rationale.

Health Authority - interaction type	Meeting date	Comments
US FDA-- Type B -20210709	09-Jul-2021 Note: The pre-NDA meeting was cancelled by Novartis based on the clear feedback provided by the FDA in the context of the pre-meeting correspondence on 06-Jul-2021 and 08-Jul-2021.	FDA confirmed that the results of EPIK-P1 may be adequate to support the approval of alpelisib for the treatment of patients with PROS. FDA indicated that the primary analysis should be based on the efficacy population (N=37), which would result in a response rate of 32.4% (95% CI: 18.0, 49.8) according to their analysis. Agreement was reached on the Type 10 NDA content as well as the timelines for submission under the RTOR Program.

The FDA's Assessment:

The FDA agrees with the Applicant's regulatory timeline and documentation of meetings as presented in Table 2, and provides the following additional comments regarding key discussions that occurred at specific meetings and other important regulatory submissions and communications.

Type B, Pre-IND Meeting – July 25, 2019

A pre-IND meeting was held to discuss the Applicant's planned development program for alpelisib in patients with PROS and a potential marketing application based on data from a single-arm clinical study of patients with severe or life-threatening PROS who have received alpelisib through compassionate use protocols as part of the expanded access program.

- Regarding the proposed study, the FDA stated this could serve as the basis of an application and advised the Applicant to collect all data to support their position that alpelisib may provide benefit to patients. The FDA stated that their decision on a marketing application and the appropriate regulatory pathway will be based on an analysis of the totality of the evidence, including an assessment of the magnitude of benefit on different endpoints, photographic or video evidence if available, the durability of the benefit, and the safety profile of the drug, given that the clinical significance of the primary endpoint of 20% volume reduction in target lesion(s) would be unclear in the absence of other supporting data. The FDA also noted that the quality and integrity of the data elements that are transcribed from patient medical records will need to be verified.
- The Applicant also proposed to conduct a single-arm clinical trial of alpelisib in pediatric and adult patients with a broader spectrum of severity of PROS manifestations (EPIK-P2). The primary objective of this study will be to evaluate the effectiveness of alpelisib by demonstration of at least 20% reduction in the sum volume of target lesions (1 to 3 lesions) by MRI, as determined by blinded independent central review, at the end of 24 weeks of treatment. The FDA did not object to the planned study design or proposed endpoints; however, the FDA noted there was insufficient justification to support the proposed dose

(50 mg daily) in the pediatric population (patients 2 to 17 years of age) and recommended the Applicant use an allometric scaling approach in popPK modeling to project the pediatric dose of alpelisib in pediatric patients that will achieve adult exposure or potentially consider switching to a body weight (mg/kg) or body surface area (mg/m^2) adjusted dose. The Applicant agreed to optimize the dose based on emerging data from later periods of the study which permit dose titration.

Breakthrough Therapy Designation – November 13, 2019
On September 18, 2019, the Applicant submitted a Breakthrough Therapy Designation (BTD) Request for alpelisib for the treatment of patients with PROS. The primary data supporting the BTD request were derived from a single published report of a case series of 19 patients (15 children and 4 adults), who had severe or life-threatening PROS or were scheduled for debulking surgery and received alpelisib under compassionate use regulations at a medical center in France. The FDA considered the submitted data based on this publication to be preliminary clinical evidence that the drug may provide clinical benefit and improvement over surgical options and supportive care therapies, as 88% of the patients in this series exhibited a ≥20% volumetric reduction in target lesions after 6 months of treatment. More importantly, lesion shrinkage was associated with other early signals of clinical benefit such as improved organ function (e.g., cardiac output, renal function), discontinuation of opioid treatment, correction of scoliosis, and the ability to walk independently. On November 13, 2019, the FDA granted BTD to alpelisib for the treatment of patients with PROS.

(b) (4)

Type B Meeting, Pre-NDA Meeting – April 2, 2020
A pre-NDA meeting was held to discuss the Applicant's proposed strategy for submission of a Type 10 NDA for alpelisib for the treatment of patients 2 years and older with PROS. FDA provided feedback regarding the contents of the NDA as outlined by the Applicant, agreed that a Type 10 NDA was acceptable as alpelisib is an approved drug and the Applicant is seeking a

new indication and proprietary name that are distinct from the original NDA, and accepted the Applicant's proposal to submit under the RTOR program. The FDA also agreed that as alpelisib has Orphan Drug Designation for the treatment of PROS and a Type 10 NDA is not considered an original application, the NDA would be exempt from PREA requirements and not subject to the amended FDARA regulations.

Type B, Pre-NDA Meeting – July 9, 2021
This pre-NDA meeting was cancelled at the Applicant's request. In the meeting minutes issued by the FDA, the FDA stated that the results of EPIK-P1 may be adequate to support the approval of alpelisib for the treatment of patients with PROS. Additionally, the FDA did not agree with the Applicant's proposed primary complete case analysis, which excluded patients without a response assessment in the pre-specified window of assessment, and stated that all 37 patients (i.e., patients with at least one target lesion at the index date) should be considered for calculation of response rate as part of the efficacy population, and those without a response assessment in the pre-specified timeframe should be considered non-responders.

General Advice Letter – February 4, 2022
The FDA issued a general advice letter to the Applicant regarding the proposed dosing for alpelisib in patients with PROS based on the EPIK-P1 study and the dosing regimens being investigated in the ongoing EPIK-P2 trial. The FDA stated that the dosing regimen administered to pediatric and adult patients receiving alpelisib via expanded access was not optimized. FDA inquired as to whether an earlier dose escalation (i.e., after 12 weeks instead of after 24 weeks) in pediatric patients (6 to 17 years of age) and a higher dose cap (i.e., 250 mg daily instead of 125 mg daily) in adolescent patients (12 to 17 years of age) could be supported by safety and efficacy data. For the EPIK-P2 study, FDA recommended that an additional dose level (starting dose of 125 mg instead of 50 mg) be studied in pediatric patients 6 to 17 years of age. The FDA also advised the Applicant to conduct dose/exposure-efficacy evaluation adjusting for potential confounding factors (e.g., frequent or hotspot PIK3CA mutations) and develop a dynamic pharmacokinetic (PK)/pharmacodynamic (PD) model to characterize longitudinal lesion response based on data collected in EPIK-P2.

Teleconference – February 11, 2022
A teleconference was held at the request of FDA to discuss the contents of the General Advice Letter described above. The Applicant communicated that data from EPIK-P1 does not support either an earlier dose increase nor an increase in dose cap in pediatric patients. The Applicant also stated an additional dose level (e.g., starting dose of 125 mg) for a small cohort of pediatric patients will be considered for incorporation into the EPIK-P2 trial. FDA acknowledged the Applicant's proposal and stated that the proposal for an additional dose cohort would be reviewed.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical data from Study EPIK-P1 were submitted to the Agency in support of NDA 215039 for alpelisib for the above proposed indication. Two clinical investigators (Drs. Marilyn Liang and Guilaume Canaud) were selected for clinical inspection.

On-site inspection of Dr. Liang revealed no significant findings. Based on the results of the inspection, Study EPIK-P1 overall appears to have been conducted adequately at Dr. Liang's site and the data generated by Dr. Liang's site in support of this NDA appear to be reliable.

At Dr. Canaud's site, source records for all 44 subjects enrolled at the site were compared to the data listing submitted to the NDA. The inspection noted that two MRI scans performed at the site were not included in the BICR assessment listing submitted to the NDA. Both scans were submitted to (b) (4) for BICR assessment by the site. One patient (b) (6) was a responder, and the missing scan was assessed as stable; the other patient was not a responder. Based on the timing of the scans and overall response assessment for each patient, the exclusion of these scans in the BICR assessment should not affect the efficacy analysis described in the review. One additional discrepancy was noted between the data submitted to the NDA and the source records, involving two instances of HbA1C values (both 5.6% and within institutional normal ranges) which were not entered in the eCRF. These discrepancies in laboratory value data capture were determined to be isolated incidents. OSI concluded that the data generated by Dr. Canaud's site appear to be acceptable in support of the proposed indication in the NDA.

Refer to the full review by OSI dated February 9, 2022 and April 1, 2022 for further details.

4.2. Product Quality

For a full discussion of product quality review issues, refer to the OPQ Integrated Quality Assessment uploaded in DARRTs on February 25, 2022. The summary below has been adapted from the executive summary of this review.

> Novartis has submitted type 10 NDA 215039 for VIJOICE (alpelisib) 50 mg, 125 mg, and 200 mg film-coated tablets for the treatment of adult and pediatric patients aged 2 years and older with PROS. Alpelisib drug substance refers to NDA 212526 (the NDA for PIQRAY). No new drug substance related information is noted in the current NDA 215039 submission; no impurity issue related to (b) (4) is noted in DS section.

The drug product formulation is derived from the approved PIQRAY (alpelisib) tablets, using the same (b) (4). The VIJOICE (alpelisib) tablets contain the same quantitatively proportional formulation as PIQRAY for the tablet core. The only change in the qualitative composition is in the pigments used in the (b) (4) filmcoating.

NDA 215039 for alpelisib film coated tablets uses the same drug product specifications for PIQRAY (alpelisib) film coated tablets with the exception for the visual appearance of the film coat and the debossing. The difference in pigments and debossing are not expected to affect the drug product dissolution, quality, and in vivo performance. The Applicant is relying upon stability data for the cross referenced and approved NDA 212526 for PIQRAY with limited stability data for the proposed 50 mg, 125 mg, and 200 mg tablets in this NDA. An expiration dating period of 36 months may be granted when stored at the proposed storage conditions.

Per 21CFR320.22(d)(2), the biowaiver request for the proposed middle strength of alpelisib tablets (yellow shades), 125 mg, is granted for the following reasons:

a) Pharmacokinetic information/data for alpelisib have been reviewed in the approved NDA 212526, showing the linear pharmacokinetics of alpelisib with respect to dose and time in the tested dosage range of 30 mg to 450 mg under fed conditions.
b) The proposed alpelisib tablets (yellow shades), 50 mg, 125 mg and 200 mg, are compositional proportional with respect to the active and inactive ingredients across strengths.
c) The proposed alpelisib tablets (yellow shades), 50 mg, 125 mg and 200 mg, are manufactured using the same manufacturing process, at the same manufacturing site, controlled via the same specifications, and packaged in the same container closure system.
d) The one time point dissolution data support that the proposed alpelisib tablets (yellow shades), 50 mg, 125 mg and 200 mg have consistent dissolution during the stability testing.

The manufacturing process for alpelisib 50 mg, 125 mg, and 200 mg (yellow shades) is based on the approved automated manufacturing process used for Piqray (NDA 212526) using the same equipment and manufacturing process. The only change between Piqray and Vijoice is the difference in the film-coating pigment for product differentiation and debossing. The microbiological risk related to manufacturing process (b) (4) were assessed in previous review for Piqray. The waiver of microbiological testing for the proposed drug product is

further supported by 12 batches of alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades) manufactured at the commercial site.

All facilities are recommended for approval based on acceptable compliancy history and relevant manufacturing experience. No pre-approval inspection is identified. The claim for categorical exclusion from an environmental assessment in accordance with 21 CFR 25.31(b) is acceptable.

In conclusion, OPQ recommends APPROVAL of NDA 215039.

Life Cycle Considerations:
(b) (4) yields were observed for the new strength- 125 mg. Yields from validation/commercial batches should be evaluated during next inspection.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

No companion diagnostic device was developed or approved for use with alpelisib for the treatment of patients with severe manifestations of PROS. The FDA does not consider a companion diagnostic test to be essential to ensure the safe and effective use of alpelisib in patients with severe manifestations of PROS. PROS is a diagnosis made on the basis of clinical features as well as identification of PIK3CA mutation. Testing for the PIK3CA mutation in PROS lesions or other patient samples is a part of routine clinical care in the diagnosis of PROS.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Alpelisib (BYL719) is a kinase inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against the α-isoform, PI3Kα. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) leads to activation of PI3Kα and downstream Akt-signaling that can promote cellular growth and transformation and the generation of tumors in in vitro and in vivo models. In 2019, alpelisib, under the tradename PIQRAY, was approved in combination with fulvestrant for the treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative and PIK3CA mutated advanced breast cancer under NDA 212526. Primary pharmacology, pharmacokinetic, general toxicology studies of up to 3 months' duration in rats and dogs, genetic toxicology, and embryo-fetal development toxicity studies in rats and rabbits conducted with alpelisib were previously reviewed by the FDA under NDA 212526. In the current NDA, the Applicant submitted literature for nonclinical pharmacology, and male and female animal fertility studies to support the approval of VIJOICE (alpelisib) for the treatment of adult and pediatric patients 2 years of age and older with severe manifestation of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy.

The Applicant submitted scientific literature and cross-referenced the pharmacology data previously submitted to NDA 212526 to support the mechanism of action of alpelisib in PROS. Original pharmacology studies submitted to NDA 212526 are relevant to the current indication since PROS encompasses a spectrum of rare disorders that causes overgrowth of parts of the body due to postzygotic mutations in PIK3CA. In the previously reviewed biochemical assays, alpelisib had similar inhibitory activity against mutant catalytic subunit alpha [p110α (H1047R, E545K)] of PIK3CA and wild type p110α. However, in cell-based assays, alpelisib had higher kinase inhibitory activity against PIK3CA mutant cancer cell lines compared to wild type cancer cells. In addition, alpelisib had anti-tumor activity in a mouse xenograft model of breast cancer with PIK3CA mutations and the anti-tumor activity correlated with inhibition of PI3K/Akt pathway. Given that activating mutations in PIK3CA are implicated in PROS, the inhibitory effects of alpelisib on PIK3CA-induced activity and growth are relevant to PROS. This was further supported with a proof-of-concept study using an in vivo inducible model of congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome (CLOVES), which is a type of PROS. Treatment of $PIK3CA^{CAGG\text{-}CreER}$ mice (*Cre*-inducible mouse model of CLOVES) with alpelisib resulted in full or partial inhibition of the PI3K/Akt/mTOR signaling pathway. Depending on when treatment was administered (e.g., at induction or post-induction of *Cre*), alpelisib prevented or improved abnormalities associated with CLOVES in mice (Venot et al. 2018). These effects were reversed when alpelisib treatment was interrupted. Overall, these results suggest that alpelisib has activity against a mouse model

of CLOVES/PROS and support the mechanism of action of alpelisib in PROS.

Alpelisib may impact growth and development in pediatric patients based on nonclinical data. In a 4-week general toxicology study, rats administered alpelisib via the intended oral route of administration had growth plate thickening and decreased trabeculae of the knee joint, dentin thinning, and degenerative odontoblasts at the dose of 30 mg/kg/day [approximately 2.8 to 1.2 times the initial recommended doses of 50 mg and 250 mg in pediatric and adult patients, respectively, based on body surface areas (BSA)]. Dentin thinning/irregular dentin was also observed in the 13-week toxicology study in rats at the high dose of 20 mg/kg/day (approximately 2 to 0.8 times the initial recommended doses of 50 mg and 250 mg in pediatric and adult patients, respectively, based on BSA). Alpelisib-induced bone and teeth findings were included in the Vijoice label under Section 8.4 as the indicated population includes patients 2 years of age and older.

The patient population for Vijoice includes patients with non-cancerous conditions. The NDA submission did not address the carcinogenicity potential of alpelisib for chronic use. Given the long life expectancy and anticipated need for prolonged treatment, it is important to address the risk of carcinogenicity from alpelisib with chronic use. Therefore, it was previously agreed (pre-NDA meeting; 4/2/2020) that carcinogenicity studies may be completed as post-marketing requirements (PMRs). As a result, a Special Protocol Assessment (SPA) for a 2-year study in rats was submitted under IND 143387 and was reviewed by the FDA on August 13, 2020. During the review cycle, two PMRs to conduct studies in rats and mice to determine the risk of carcinogenicity from alpelisib were negotiated with the Applicant.

The Applicant evaluated the effects of alpelisib on fertility and early embryonic development in male and female rats in two separate studies. Toxicokinetic evaluations were not conducted in fertility studies. In a fertility and early embryonic study, female rats were treated orally with vehicle or alpelisib at 3, 10, and 20 mg/kg/day for up to 42 days (4-weeks prior to pairing, during pairing, and up to Gestation Day 6). Vehicle- or alpelisib-treated females were mated with untreated males. In treated females at the high dose of 20 mg/kg/day, alpelisib increased pre- and post-implantation losses, leading to reduced numbers of implantation sites and live embryos. These findings were observed at doses approximately 2.4 to 0.8 times the initial recommended doses of 50 mg and 250 mg in pediatric and adult patients, respectively, based on BSA. There were no findings noted in estrous cycle in the female fertility study; however, histopathology changes observed in female reproductive organs in the repeat-dose general toxicology studies of up to 13-week duration, included vaginal atrophy and estrous cycle variations in rats at doses ≥ 6 mg/kg/day (approximately 0.7 to 0.2 times the initial recommended doses of 50 mg and 250 mg in pediatric and adult patients, respectively, based on BSA). In a separate dedicated fertility study, males received oral administration of vehicle or

alpelisib at doses of 3, 10, and 20 mg/kg/day for 10 weeks prior to pairing, during co-habitation with untreated females, and post-pairing. In male rats, alpelisib reduced weights of seminal vesicles and prostate, which correlated with atrophy and/or reduced secretion in prostate and seminal vesicles at ≥ 10 mg/kg/day (approximately 1.2 to 0.4 times the initial recommended doses of 50 mg and 250 mg in pediatric and adult patients, respectively, based on BSA). Despite these changes, alpelisib had no remarkable effects on male fertility and reproductive performance, including sperm count and motility parameters at doses up to 20 mg/kg/day. Additionally, pairing alpelisib-treated male rats with untreated females had no effect on embryo-fetal development in the untreated females. Fertility findings are described in the label in Section 13.1.

Embryo-fetal development (EFD) studies were conducted with alpelisib in pregnant rats and rabbits. These studies were reviewed under NDA 212526. Administration of alpelisib to pregnant animals during organogenesis caused embryo-fetal mortality (post-implantation loss), reduced fetal weights, and increased incidences of fetal malformation at maternal doses approximately below or equivalent to the recommended doses of 50, 125, and 250 mg in pediatric and adult patients, based on BSA. Based on the data from the EFD studies and the fertility and early embryonic study in female rats, a warning for embryo-fetal toxicity is included in the label for Vijoice.

The EFD studies previously reviewed under NDA 212526 contained toxicokinetic data; however, the fertility studies submitted to the current NDA did not include toxicokinetic evaluations. Additionally, at the time of this review, there is no available human PK data in patients with PROS who were exposed to alpelisib. Thus, animal to human comparisons in the review and label were based on human equivalent dose based on body surface areas. The proposed initial recommended dosage is 50 mg/day or 250 mg/day in children 2 to < 18 years old or in adults (≥ 18 years), respectively. Considering that EFD and fertility studies are generally not relevant to children under 12 years old, estimated safety margins were calculated using an initial dose of 50 mg and a BSA of 1 m^2 for adolescents 12 to 17 years old; and the initial dose of 250 mg and a BSA of 1.6 m^2 for adults (≥ 18 years old). For animal to human comparisons for growth and development findings in general toxicology studies, estimated safety margins were calculated using an initial dose 50 mg and a BSA of 0.8 m^2 for pediatric patients 2 years old or older; and the initial dose of 250 mg and a BSA of 1.6 m^2 for adults. Additionally, estimated safety margins were reported as a range, since the recommended dose in pediatric patients 6 to < 18 years old may increase from 50 mg/day to 125 mg/day after 24 weeks of treatment.

Recommendation:
The nonclinical data submitted to this NDA and cross-referenced data from NDA 212526 are adequate to support the approval of alpelisib for the proposed indication. We recommend post-marketing requirements to assess the carcinogenicity potential of alpelisib for chronic use.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
All relevant information was provided within the Piqray (alpelisib) NDA 212526 submission. The nonclinical pharmacology/toxicity profile for alpelisib has not changed and previously submitted results support the treatment of patients with PROS with the intended dose regimen of 50 mg once daily in pediatric and 250 mg once daily in adult patients.

The FDA's Assessment:

The FDA agrees with the Applicant that NDA 212526 was cross-referenced for nonclinical data and that the nonclinical pharmacology/toxicology profile for alpelisib has not changed. While the previous nonclinical data, together with submitted fertility studies, support the new indication from the pharmacology/toxicology perspective, we refer to the clinical and clinical pharmacology portions of the review for discussion of the appropriateness of the intended dosage regimen for patients with PROS.

5.3. Pharmacology

Primary pharmacology

The Applicant's Position:
All relevant information was provided within the Piqray NDA. Additional information (a brief overview of the transporter study (DMPK R2000201) is provided in Nonclinical-overview-addendum1 (Please see Section 5.4 below). No new information is provided in the current submission.

The FDA's Assessment:
The FDA agrees that primary pharmacology data were previously submitted and reviewed by the FDA under NDA 212526. These data are relevant to the proposed PROS indication as gain-of-function mutations in PIK3CA play a pivotal role in driving the disease. In addition, the Applicant provided a reference by Venot et al. (2018) as proof-of-concept to support the mechanism of action of alpelisib in PROS. FDA's review focused on the nonclinical data for alpelisib described in this publication. The highlights of the nonclinical data are shown below:

"Targeted therapy in patients with PIK3CA-related overgrowth syndrome" Venot *et al.* *Nature. 2018 Jun; 558(7711): 540-546*

Characterization of mouse model of PROS/CLOVES

The authors developed an inducible PIK3CA$^{CAGG\text{-}CreER}$ mouse model, in which animals expressed active PIK3CA transgene after induction with tamoxifen. Characterization of the model was conducted using various techniques, including survival curves, whole body magnetic resonance imaging (MRI), immunohistochemistry and immunofluorescence, and Western Blots:

- Induction of PIK3CA resulted in mortality
    - A single administration of high dose (40 mg/kg) tamoxifen (the inducer) resulted in 50% mortality by Day 9 post-induction.
    - PIK3CA$^{CAGG\text{-}CreER}$ mice induced with a low dose (4 mg/kg) tamoxifen died two months post-induction.
- Induction of PIK3CA resulted in phenotypic changes of PROS/CLOVES
    - A single administration of high dose (40 mg/kg) tamoxifen induced scoliosis, vessel and organ abnormalities, kidney cysts and muscle hypertrophy.
    - A single administration of low dose (4 mg/kg) tamoxifen induced asymmetrical overgrowth of extremities, lipomatous tumors and vascular abnormalities.
    - In general, increased proliferation (increased Ki67+ staining) were noted but no effects in apoptosis or senescence were observed.
    - Tissue analyses showed enhanced expression of mutant p110α, and increased phosphorylation of AKT (Ser^{473}), AKT (Thr^{308}) and S6RP in lysates from selected tissues (e.g., liver, heart, and muscles) of PIK3CA$^{CAGG\text{-}CreER}$ mice, suggestive of Akt/mTOR pathway activation, compared to PIK3CA^{WT}.

Effects of Alpelisib treatment

PIK3CA$^{CAGG\text{-}creER}$ mice were administered 50 mg/kg/day alpelisib orally on day of induction, (termed as preventive) and up to 40 days or 7-days post-induction, when PROS phenotype by MRI was already observed (therapeutic).

- All PIK3CA$^{CAGG\text{-}creER}$ mice receiving preventive treatment survived while on alpelisib, whereas vehicle treated PIK3CA$^{CAGG\text{-}creER}$ animals died within 15 days of post-induction. Additionally, alpelisib-treated mice exhibited normal tissue and blood vessels, reduced cell proliferation and inhibition of Akt/mTOR signaling pathway (e.g., P-AKT and P-S6RP) in tissue lysates. Following alpelisib discontinuation, animals died within 10 days after drug interruption.
- PIK3CA$^{CAGG\text{-}creER}$ mice receiving therapeutic treatment showed improvement of disease abnormalities when compared to PIK3CA^{WT} mice. Alpelisib also reduced proliferation and attenuation of Akt/mTOR pathway.
- In PIK3CA$^{CAGG\text{-}creER}$ mice treated with low dose tamoxifen to induce PROS phenotype,

alpelisib reduced tumors within 2 weeks and this effect was reversible when drug was withdrawn.

In summary, in an inducible mouse model of PROS/CLOVES (PIK3CA$^{CAGG\text{-}CreER}$), alpelisib downregulated PI3K signaling activity and either prevented onset of PROS phenotype or improved abnormalities associated with PROS, depending on when treatment was administered. Dose interruption reversed effects noted with alpelisib.

See Section 5.4 regarding FDA's assessment of transporter study data.

5.4. ADME/PK

The Applicant's Position:
The majority of ADME/PK data and relevant information was submitted within the Piqray NDA. The substrate specificity of alpelisib on additional transporters was studied and demonstrated that alpelisib is not a substrate of Bile Salt Export Pump (BSEP), Multidrug Resistance-associated Protein 2 (MRP2) and the Human Multidrug and Toxin Extrusion-1 (MATE1) (nonclinical-overview-addendum1, DMPK R2000201).

The FDA's Assessment:
The FDA agrees that the majority of ADME/PK data were submitted and reviewed under NDA 212526. The new in vitro clinical pharmacology studies submitted were not reviewed by the pharmacology/toxicology team. See the Clinical Pharmacology section for comment on in vitro drug interaction studies.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:
All relevant information was submitted within the Piqray NDA. No new information is provided in the current submission.

The FDA's Assessment:
The FDA agrees with the Applicant that no new toxicology information is provided in the current submission. The Applicant has cross-referenced the general toxicology data previously submitted to NDA 212526 for PIQRAY.

In the 4-week general toxicology study, rats administered alpelisib had growth plate thickening and decreased trabeculae of the knee joint, dentin thinning, and degenerative odontoblasts at

the dose of 30 mg/kg/day. Dentin thinning/irregular dentin was also observed in the 13-week toxicology study in rats at the high dose of 20 mg/kg/day. Since alpelisib effects on growth may be relevant to a pediatric population, this information was included in the label under Section 8.4.

5.5.2. Genetic Toxicology

The Applicant's Position:
All relevant information was submitted within the Piqray NDA. No new information is provided in the current submission.

The FDA's Assessment:
The FDA agrees.

5.5.3. Carcinogenicity

The Applicant's Position:
A carcinogenicity program is ongoing. The program consists of a 2-year bioassay in rats, for which the protocol was submitted to the FDA for Special Protocol Assessment (SPA), and will potentially be followed by a 6-month study in Tg rasH2 mice, depending on the outcome of the rat study. The results of the study will be submitted to the FDA in 2024.

The FDA's Assessment:
The FDA agrees. Two nonclinical post-marketing requirements (PMRs) for rodent carcinogenicity studies were communicated to the Applicant.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Study title / Study 2070119/ eCTD location: M4.2.3.5 Reproductive and developmental toxicity/ eCTD Section 4.2.3.5.1 Study type : Oral (Gavage) Study of Fertility in the Male Rat Key Drug-related Adverse Findings: Adverse reduced body weight gain at 10 and 20 mg/kg/day. Accessory glands weights (seminal vesicles, prostate) reduced at 10 and 20 mg/kg/day and correlated microscopically with atrophy and/or reduced secretion in prostate and seminal vesicles, respectively. Male fertility parameters were unaffected. NOAEL = 20 mg/kg/day for fertility and 3 mg/kg/day for general toxicity

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	3, 10, or 20 mg/kg/day- Daily
Route of administration:	Oral (gavage)
Formulation/Vehicle:	Aqueous 0.5% (w/v) Methyl cellulose solution
Species/Strain:	Crl:WI (Han) rats
Number/Sex/Group:	24/male/; 24 female (female untreated and used for mating only
Age:	7-8 weeks (males), 9-10 weeks (females)
Satellite groups:	None

Study Design: Study 2070119

Group	Dose (mg/kg/day)	Dose Concentration (mg/mL)	Animal Numbers	
			Males	Females[1]
1 (Control)	0	0	R0001-R0024	R0401-R0424, R0800
2 (Low)	3	0.6	R0101-R0124	R0501-R0524, R0799
3 (Intermediate)	10	2	R0201-R0224	R0601-R0624
4 (High)	20	4	R0301-R0324	R0701-R0724

[1]Females were not dosed and were used for mating purposes only

Study title / Study 2070120/ eCTD location: M4.2.3.5 Reproductive and developmental toxicity/ eCTD Section 4.2.3.5.1.
Study type : Oral (Gavage) Study of Fertility and Early Embryonic Development in the Female Rat
Key Drug-related Adverse Findings: Reduced body weight gain at all dose levels. At 20 mg/kg/day increased pre- and post-implantation losses led to reduced numbers of implantation sites and live embryos. NOAEL = 10 mg/kg/day for fertility, no NOAEL for female toxicity.
GLP compliance: Yes

Methods	
Dose and frequency of dosing:	3, 10, or 20 mg/kg/day- Daily
Route of administration:	Oral (gavage)
Formulation/Vehicle:	Aqueous 0.5% (w/v) Methyl cellulose solution
Species/Strain:	Sprague Dawley Rats? Crl:WI (Han) rats
Number/Sex/Group:	24/female; 24/male untreated and used for mating only

Age:	Females 9 to 10 weeks old at the start of dosing. Males were 10 to 11 weeks old at pairing for mating.
Satellite groups:	none

Study Design (Study 2070120)

Group	Dose (mg/kg/day)	Dose Concentration (mg/mL)	Animal Numbers	
			Males[a]	Females
1 (Control)	0	0	R0001-R0024	R0401-R0413, R0415, R0417- R0424, R0798-R0799b
2 (Low)	3	0.6	R0101-R0124	R0501-R0524
3 (Intermediate)	10	2	R0201-R0224	R0601-R0624
4 (High)	20	4	R0301-R0324	R0701-R0724

a Males were not dosed; used for mating purposes only
b Based on predose estrous cycle data, R0414 and R0416 (Group 1 females) were swapped with spare animals R0798 and R0799 before the initiation of dosing.

The FDA's Assessment:

The FDA agrees with the Applicant's summary of the design and results of the fertility studies. We also note that fertility studies did not include toxicokinetic evaluations. Additional details of the study design and results are provided below:

Male Fertility (Study# 2070119)
Male rats were dosed with alpelisib for up to 99 days [10 weeks prior to pairing (pre-pairing), during pairing, and post-pairing phases]. Untreated female rats were used for mating purposes only. Males were euthanized on Day 14/15 of post-pairing phase and mated females were euthanized on GD 13.

Observations and Results: changes from control

Parameters	**Key Findings**
Mortality	There was no unscheduled death during study.
Clinical Signs	Unremarkable

<table>
<tr><td>Body Weights</td><td>

Reduced mean body weight versus control was observed at pre-pairing, pairing and post-pairing phases of up to -12% at 10 mg/kg/day, starting on Day 29 of pre-pairing phase; and up -21% at 20 mg/kg/day, starting on Day 8 of pre-pairing phase.
Reduced mean body weight gain versus control was -18%, -35% and -60% for 3, 10, and 20 mg/kg/day, respectively, from Day 1 to 71 of pre-pairing phase. Reduced body weight gain versus control were -66% and -78% for 10 and 20 mg/kg/day, respectively, from Day 3 to 14 of post-pairing phase. No change was noted during pairing phase.
Changes in body weight and body weight gain were associated with reduced food consumption.

</td></tr>
<tr><td>Food Consumption</td><td>Reduced food intake at ≥ 10 mg/kg/day (up to -23%) during pre-pairing phase. Food intake was reported only for pre-pairing phase.</td></tr>
<tr><td>Organ weights</td><td>
Changes in absolute organ weights relative to control
<table>
<tr><th>Dose (mg/kg)</th><th>Prostate</th><th>Seminal Vesicle</th></tr>
<tr><td>3</td><td>↓9%</td><td>↓7%</td></tr>
<tr><td>10</td><td>↓25%</td><td>↓23%</td></tr>
<tr><td>20</td><td>↓41%</td><td>↓41%</td></tr>
</table>
↓-Decrease; bold: statistically significant from control
</td></tr>
<tr><td>Reproductive performance</td><td>

Mating occurred on Days 1 to 13, with majority occurring within 4 days of cohabitation for all dose levels and control.
Mating, fecundity, and fertility indices were unremarkable compared to control group.
There were no remarkable differences between female rats mated with the control (vehicle treated males) and those mated with alpelisib-treated males in mean number of corpora lutea, implantation sites, pre- and post-implantation losses, and the mean number of live embryos at scheduled cesarean section.

</td></tr>
<tr><td>Sperm Assessment</td><td>Reduced caudal epididymal absolute weight (CEW) at 20 mg/kg, however, the CEW relative to body weight was not changed. Alpelisib-treatment did not have a remarkable effect on sperm count or motility.</td></tr>
</table>

<table>
<tr><td>Histopathology</td><td>In males post-pairing, microscopic findings in the prostate and seminal vesicles included decreased secretion/atrophy in the prostate and decreased acinar secretion in the seminal vesicles at ≥ 10 mg/kg (table below). The decrease in secretions correlated with the reduced weights in these organs. Despite these findings, reproductive performance and fertility were not impaired.
<table>
<tr><td>Alpelisib (mg/kg/day)</td><td>0</td><td>3</td><td>10</td><td>20</td></tr>
<tr><td>Number examined</td><td>24</td><td>24</td><td>24</td><td>24</td></tr>
<tr><td>Prostate
Secretion, decreased/atrophy</td><td colspan="4"></td></tr>
<tr><td>Minimal</td><td>--</td><td>--</td><td>5</td><td>2</td></tr>
<tr><td>Slight</td><td>--</td><td>--</td><td>5</td><td>12</td></tr>
<tr><td>Moderate</td><td>--</td><td>--</td><td>1</td><td>9</td></tr>
<tr><td>Seminal Vesicle
Secretion, decreased/atrophy</td><td colspan="4"></td></tr>
<tr><td>Minimal</td><td>--</td><td>1</td><td>1</td><td>6</td></tr>
<tr><td>Slight</td><td>--</td><td>--</td><td>8</td><td>7</td></tr>
<tr><td>Moderate</td><td>--</td><td>--</td><td>--</td><td>2</td></tr>
</table>
--: indicates no finding</td></tr>
</table>

Female Fertility (Study# 2070120)

Female rats were dosed with alpelisib for up to 42 days [4 weeks prior to pairing (pre-pairing), during the pairing phase, and up to Gestation Day (GD) 6]. Untreated male rats were used for mating purposes only. Mated females were sacrificed on GD 13.

Observations and Results: changes from control

Parameters	Key Findings
Mortality	One female at 20 mg/kg/day was sacrificed moribund on pre-pairing Day 6 after five doses. Clinical signs included piloerection, thinness, hunched posture, skin tenting and weight loss. The cause of moribund condition was undetermined.
Clinical Signs	There were no remarkable alpelisib-related clinical observations in surviving animals.

<table>
<tr><td>Body Weights</td><td>

Reduced mean body weight versus control was observed at pre-pairing and gestation phases of up to -8% at 10 mg/kg/day, starting on Day 22 of pre-pairing phase; and up -13% at 20 mg/kg/day, starting on Day 15 of pre-pairing phase.
Reduced mean body weight gain versus control was -24%, -39% and -64% for 3, 10, and 20 mg/kg/day, respectively, during pre-pairing phase; however, no significant change was noted at end of gestation period.

</td></tr>
<tr><td>Food Consumption</td><td>Pre-pairing phase: A -15% decrease on Days 1 to 4 at 20 mg/kg/day.
Gestation phase: A -12% decrease from Day 0 to 13 at 20 mg/kg/day.</td></tr>
<tr><td>Reproductive Performance</td><td>

No effects were noted in mean number of estrous cycles or estrous cycle length with alpelisib during pre-dose and pre-pairing.
Mating occurred on Days 1 to 7, with majority occurring within 4 days of cohabitation for all dose levels and control.
Reproductive performance indices for mating, fecundity and fertility were unremarkable compared to control group.

</td></tr>
<tr><td>Necropsy findings Cesarean Section Data</td><td>Treatment with alpelisib at 20 mg/kg/day resulted in decreased number of implantation and increased percentage of post-implantation loss, and consequently a reduced number of live embryos compared to controls.

Summary of cesarean section data at scheduled sacrifice
<table>
<tr><th></th><th colspan="4">Alpelisib (mg/kg/day)</th></tr>
<tr><th>Cesarean (C) Section Parameters</th><th>0</th><th>3</th><th>10</th><th>20</th></tr>
<tr><th># Females pregnant at Cesarean Section</th><th>23</th><th>21</th><th>24</th><th>21</th></tr>
<tr><td>Corpora Lutea (mean)</td><td>13.8</td><td>13.2</td><td>12.8</td><td>13.1</td></tr>
<tr><td>Implantation Sites (mean)</td><td>12.4</td><td>12.2</td><td>11.6</td><td>10.4</td></tr>
<tr><td>Pre-implantation Loss (mean)</td><td>1.4</td><td>1.0</td><td>1.3</td><td>2.7</td></tr>
<tr><td>Pre-implantation Loss (%)</td><td>10.1</td><td>7.6</td><td>10.2</td><td>20.6*</td></tr>
<tr><td>Early Resorptions (mean)</td><td>0.8</td><td>0.3</td><td>0.8</td><td>3.1*</td></tr>
<tr><td>Late Resorptions (mean)</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Post-implantation Loss (mean)</td><td>0.8</td><td>0.3</td><td>0.8</td><td>3.1</td></tr>
<tr><td>Post-implantation Loss (%)</td><td>6.5</td><td>2.5</td><td>6.9</td><td>29.8*</td></tr>
<tr><td>Live Embryos</td><td>11.6</td><td>12.0</td><td>10.8</td><td>7.4*</td></tr>
</table>
*Statistically significant from concurrent controls</td></tr>
</table>

5.5.5. Other Toxicology Studies

The Applicant's Position:

As a follow-up of a previous study to investigate skin toxicity in Brown Norway rats [Study 1670271], two studies were conducted to further investigate the time course of the changes [Study 1770766] and [Study 1870156], using the same rat strain and same daily dose levels. In the first of these two studies [Study 1770766], the period between 3 and 21 Days was investigated, and in the second study [Study 1870156] timepoints shorter than 3 days were considered.

In these two studies, essentially comparable pattern of changes induced by alpelisib treatment was observed as in the first 4-week study [Study 1670271]. Sequential immune activation steps in peripheral lymph nodes and skin preceded clinically apparent skin changes, and CD8+ CD163+, NK, and CD8+ T cells appear to be key immune cells driving the skin changes. Of the earliest markers, increases in leptin seen on day 1, followed by fractalkine, IP-10 and MIP-1α beginning on day 2, with decreases in LIX and RANTES on day 3 were observed.

Thus, broadly these findings are indicative of a T-cell dependent hypersensitivity reaction in rats.

The FDA's Assessment:
The FDA agrees with the conclusions stated above by the Applicant.

X	X
G. Sachia Khasar, PhD Primary Reviewer	Claudia P. Miller, PhD Acting Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Alpelisib is an phosphatidylinositol-3-kinase (PI3K) inhibitor with inhibitory activity predominantly against PI3Kα approved for the treatment of adult patients with advanced or metastatic breast cancer under NDA 212526 with brand name of Piqray. The current Type 10 NDA submission is for alpelisib for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy.

The safety and efficacy of alpelisib in adult and pediatric patients with PROS was demonstrated in a single-arm clinical study of 57 patients who were treated as part of an expanded access program for compassionate use, Study CBYL719F12002, also referred to as EPIK-P1. Clinical pharmacology information for alpelisib is based on data from NDA 212526 as no clinical pharmacology data were collected in EPIK-P1.

The proposed alpelisib dosage in adult patients is 250 mg of alpelisib administered orally once daily (QD) with food. The proposed starting dosage in pediatric patients is 50 mg of alpelisib administered orally QD with food. This pediatric dosage may be titrated to 125 mg QD after ≥ 24 weeks of alpelisib treatment for patients aged 6 years and older based on clinical response and tolerance, and the dose may be further increased to 250 mg QD when the patient turns 18 years old.

The review team recommends that a dose optimization study in pediatric patients aged 6 to 17 years old be conducted as a postmarketing commitment (PMC). This recommendation is based on concerns that the proposed pediatric initial dose of 50 mg may be subtherapeutic given that it is 1/5 of the adult dose and a lower response rate was observed in pediatric patients aged 6 – 11 years old when compared to the response rate observed in adults who received an alpelisib dose of 250 mg.

The Office of Clinical Pharmacology has reviewed the information contained in this NDA and recommends approval from a clinical pharmacology perspective, with a PMC to further assess dose optimization to be completed in the post-marketing setting. The key review issues with the specific recommendations and comments are summarized below:

Table 3. Clinical Pharmacology Review Issues and Recommendations.

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from the single-arm clinical study of patients who received alpelisib through an expanded access program for compassionate use, CBYL719F12002 (EPIK-P1). EPIK-P1 demonstrated clinically meaningful improvements in lesion response, defined as ≥20% reduction in target lesion volume at week 24 of alpelisib treatment in patients with PROS. The FDA considered confirmed response rate as the primary regulatory endpoint for assessment of effectiveness, along with duration of response.
General dosing instructions	The proposed adult dosage regimen of 250 mg QD is acceptable based on efficacy and safety results from Study EPIK-P1.
Dosing in pediatric patients	The Applicant proposed an initial dosage of 50 mg QD in pediatric patients aged 2 – 17 years old. For patients ≥6 years old, the dose may be increased to 125 mg based on clinical response after patients have been on alpelisib 50 mg for at least 24 weeks. When patients turn 18 years old, their dose may be gradually increased to 250 mg.

Table 4: Post-Marketing Requirements and Commitments.

PMR or PMC	Key issue(s) to be addressed	Rationale	Key Considerations for Design Features
PMC	Dose Optimization	Alpelisib will be approved for PROS without clinical pharmacology data in this NDA to guide dosing, as all clinical data for PROS come from single-arm clinical study based on an expanded access program for compassionate use, EPIK-P1. The proposed starting dose of alpelisib 50 mg may be subtherapeutic in pediatric patients 6 to 17 years old, as it is only 1/5 of the adult dose of 250 mg. Additionally, a	Study a higher starting dose of alpelisib (e.g., 125 mg QD) as compared to the 50 mg starting dose in pediatric patients age 6 to 17 years old to evaluate comparative pharmacokinetics, safety, and clinical outcomes for dose optimization in this patient population.

		lower response rate was observed in pediatric patients 6 – 11 years old at the starting dose of 50 mg when compared to the response rate in adults at dose of 250 mg. A dose optimization study should be conducted in pediatric patients 6 to 17 years old.	

6.2. Summary of Clinical Pharmacology Assessment

All relevant information to support the clinical pharmacology profile of alpelisib was submitted within the Piqray NDA.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data and The Applicant's Position:
The results of the comprehensive clinical pharmacology program conducted for alpelisib were submitted within the Piqray NDA and subsequently reflected in the approved label for the breast cancer indication (Piqray USPI). Novartis is also conducting drug-drug interaction (DDI) studies which were agreed upon as post-marketing commitments (PMCs) at the time of approval of Piqray for the breast cancer indication (PMC 3573-2 and PMC 3573-3). Given the previous agreement with the FDA and the real world nature of the retrospective chart review study EPIK-P1, no new information concerning pharmacology and clinical pharmacokinetics in the target population was generated nor available for the current NDA submission.

Novartis therefore considers that the clinical pharmacology program is sufficient to support the proposed indication in target population.

The FDA's Assessment:
The FDA agrees with Applicant's position and acknowledges the previous agreement as well as the retrospective nature of the data collection in the EPIK-P1 single-arm clinical study. No new information pertinent to pharmacology and clinical pharmacokinetics in the target PROS population was generated nor available for the current NDA submission.

However, the current submission provided insufficient data to support that the Applicant's proposed dosage of 50 mg QD in all pediatric patients irrespective of age or weight is an optimal dosage. At the initial pediatric dose of 50 mg, 1/5 of the adult dose, the pediatric exposure is predicted to be less than 1/3 of the adult exposure at 250 mg QD dosage based on adult population PK model. As a result, a PMC study to evaluate a higher starting dose (e.g.,

125 mg QD) in pediatric patients 6 years and older in the ongoing EPIK-P2 trial will be issued with this NDA approval.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
The recommended dose of alpelisib for the treatment of PROS in pediatric patients (2-17 years) is 50 mg (one 50 mg tablet) taken orally once daily with food and in adult patients (≥ 18 years) is 250 mg (one 200 mg tablet and one 50 mg tablet) taken orally once daily with food. A dose increase can be considered in pediatric patients ≥ 6 years for response optimization based on physician's discretion, after at least 24 weeks of treatment with alpelisib. In pediatric patients ≥ 6 years, the dose can be gradually increased from 50 mg up to 125 mg. When a pediatric patient turns 18 years, a gradual dose increase up to 250 mg can be considered. Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs for the treatment of PROS.

The Applicant's Position:
The recommended starting doses in pediatric and adult patients are based on those used by a treating physician in context of a compassionate use program called a nominative Temporary Authorization for Use (ATU) in France (Venot et al. 2018), which were subsequently used more broadly in compassionate use programs outside of France (as per the recommendation in the Novartis Managed Access Program [MAP]), and later confirmed to be associated with significant clinical improvement in patients with PROS without major safety concerns in EPIK-P1 study. Even though no PK data are available in PROS patients (≥ 2 years of age) given the real world nature of EPIK-P1 study, the clinical efficacy and safety results from EPIK-P1 (N=57), support the use of 50 mg once daily (with food) in pediatric patients and 250 mg once daily (with food) in adult patients.

The FDA's Assessment:
The FDA agrees with the Applicant's proposed recommended dosage of alpelisib 250 mg QD in adult patients. The FDA has concerns with the Applicant's proposed recommended dosage of alpelisib 50 mg QD in pediatric patients regardless of age. See Section 6.3.2.2 for detailed information on FDA considerations for the proposed pediatric dosage.

6.2.2.2. Therapeutic Individualization

Data:
The doses in pediatric and adult patients with PROS are different; details are provided in Section 6.2.2.1.

The Applicant's Position:

Based on the data from adult cancer patients, no clinically significant differences in the pharmacokinetics of alpelisib were predicted based on age (21 to 87 years), sex, race/ethnicity (Japanese or Caucasian), body weight (37 to 181 kg), mild to moderate renal impairment (CLcr 30 to < 90 mL/min based on the Cockcroft-Gault formula), or mild to severe hepatic impairment (Child-Pugh Class A, B, and C). The effect of severe renal impairment (CLcr < 30 mL/min) on the pharmacokinetics of alpelisib is unknown.

Dose modifications may be needed (e.g., for the management of adverse events (AEs), optimization of clinical responses, etc.) considering that the treatment of patients with alpelisib is anticipated to be long-term. Based on data from EPIK-P1, 10/28 (35.7%) pediatric patients ≥ 6 years of age, had at least one dose increase of alpelisib from their respective starting doses; 4/18 (22.2%) of adult patients had at least one dose reduction for safety management [PROS EPIK-P1-CSR-Table 10-26]. As such, dose modifications can be considered to optimize clinical response.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position that dose modifications may be needed (e.g., for the management of adverse reactions (ARs), optimization of clinical responses, etc.) considering the low starting dose of alpelisib in pediatric patients and anticipated long-term treatment of patients with alpelisib.

See Section 6.2.2.1 for FDA's assessment for pediatric dosing.

PIK3CA Mutational Spectrum and Response to Alpelisib

In EPIK-P1, the presence of a PIK3CA mutation was determined by local testing (78% NGS, 14% RT-PCR, and 8% Other) in tissue (81%) or another sample type (19%). Over 80% of activating PIK3CA mutations in cancer and PROS cluster at three hotspots: E542 and E545 in the helical domain and H1047 in the kinase domain (Madsen et al 2018). The remaining PIK3CA mutations comprise a diverse and less characterized subset. Biological differences among the various mutations in PROS may influence the phenotype (Mirzaa et al 2016, Keppler-Noreuil et al 2014, Madsen et al 2018). To conduct exploratory subgroup analyses, the Applicant categorized PIK3CA mutations in "frequent" (reported in ≥2% PROS cases) and "less-frequent" (reported in <2% PROS cases) based on a literature search on prevalence of different mutations in PROS patients. According to this categorization (i.e., based on a cutoff of 2%), H1047R, E542K, H1047L, E545K, E453K, and C420R mutations were classified as frequent mutations. This group includes the 3 most common PIK3CA hotspot mutations in breast cancer (e.g., H1047R, E542K, E545K), and which have strong oncogenic potential based on nonclinical models described in published literature (Gymnopoulos et al 2007). Other PIK3CA mutations were classified as less-

frequent, provided the mutations were predicted to be activating. Table 5 shows the distribution and key features of PIK3CA mutations within the efficacy population (N=37), as well as confirmed responses at 24 weeks.

Of 25 patients with frequent mutations, 32% were adult and 68% were pediatric. Five of the 6 mutations classified as "frequent" by the Applicant were observed in the study (i.e., all except the E453K mutation). Of 12 patients with "less-frequent" mutations (11 of which were unique), 25% were adult and 75% were pediatric patients. All responders (7 pediatric and 3 adult patients) had "frequent" mutations and the CLOVES PROS subtype, and the PIK3CA mutations found in these patients were located throughout the coding sequence, spanning from the C2 to the kinase domain. The percent of somatic mosaicism (as obtained from patient CRFs) was variable, ranging from 3 to 50% (not shown).

Table 5: Distribution and Key Features of PIK3CA mutations and Response to Alpelisib within the Efficacy Population (N=37)

Protein Domain[&]	PIK3CA Mutation	PROS subtype	Adult or Pediatric	Confirmed Response at 24 weeks
Frequent Mutations (N=25)				
C2 domain (N=5)	C420R (N=5)	CLOVES	Adult	**Yes**
		CLOVES	Pediatric	No
		CLOVES	Pediatric	No
		FIL	Pediatric	No
		FIL	Pediatric	No
Helical Domain (N=12)	E542K (N=8)	CLOVES	Adult	No
		CLOVES	Adult	No
		CLOVES	Adult	No
		CLOVES	Adult	No
		CLOVES	Pediatric	**Yes**
		CLOVES	Pediatric	**Yes**
		CLOVES	Pediatric	No
		OTHER	Pediatric	No
	E545K (N=4)	CLOVES	Adult	**Yes**
		CLOVES	Pediatric	**Yes**
		CLOVES	Pediatric	**Yes**
		CLOVES	Pediatric	No

Protein Domain[&]	PIK3CA Mutation	PROS subtype	Adult or Pediatric	Confirmed Response at 24 weeks
Kinase domain (N=7)	H1047L[&] (N=2)	CLOVES	Pediatric	**Yes**
		CLOVES	Pediatric	**Yes**
	H1047R (N=5)	CLOVES	Adult	**Yes**
		CLOVES	Adult	No
		CLOVES	Pediatric	**Yes**
		CLOVES	Pediatric	No
		FIL	Pediatric	No
Helical and Kinase domains (N=1)	E542K + H1047R (N=1)	CLOVES	Pediatric	No
Less-frequent Mutations (N=12)				
P85 domain (N=1)	P104L(N=1)	CLOVES	Adult	No
---	G106V (N=1)	CLOVES	Pediatric	No
----	E110DEL (N=1)	KTS	Pediatric	No
C2 domain (N=2)	N345K (N=2)	CLOVES	Adult	No
		CLOVES	Pediatric	No
Helical domain (N=3)	E545A (N-1)	CLOVES	Pediatric	No
	E545G (N=1)	CLOVES	Adult	No
	Q546R (N=1)	MCAP	Pediatric	No
-----	E726K (N=1)	CLOVES/MCAP	Pediatric	No
Kinase domain (N=3)	T1025A (N=1)	CLOVES/MCAP	Pediatric	No
	N1044K (N=1)	CLOVES	Pediatric	No
	H1047A (N=1)	Other	Pediatric	No

Source: Reviewer exploratory analyses. Frequent and less-frequent mutations as defined by the Applicant; Domain information is based on PROSITE [Sequence P42336 [UniProtKB/Swiss-Prot (release 2021_04 of 29-Sep-21]. C3140A>T mutation was initially classified by the Applicant as less-frequent. This mutation was reclassified as frequent upon FDA review (it corresponds to p. H1047L); Patients without any response assessment at week 24 were considered non-responders. All mutations were predicted to be activating based on literature and/or public databases (e.g., COSMIC).

These results contrast with the Applicant's Table 16 (Section 8.1.2), showing response in one patient with a less-frequent mutation. Upon FDA review, it was determined that the mutation identified in this patient's sample was listed in the CRF at nucleotide level (C3140A>T) and corresponded to a frequent mutation when described at protein level (p. H1047L).

Because of potential differences in biological properties and the lack of responses in the subgroup of patients with less-frequent mutations, FDA requested available evidence of alpelisib activity against these mutations. In response to the FDA information request (02/02/2022), the Applicant provided nonclinical data from literature and internal databases that included cancer cell lines and mouse xenograft models, as well as kinase activity screens. Collectively, the submitted information supports that less-frequent PIK3CA mutations are sensitive to alpelisib, although to a lesser extent compared to frequent mutations (for details, refer to Appendix, Section 19.4.3). Moreover, the clinical reviewer evaluated narratives that provide some early, descriptive information regarding changes in PROS-related symptoms in pediatric and adult patients with less-frequent mutations (for details, refer to Clinical review, Section 8.1.2, subsection "Additional Analyses Conducted on the Individual Trial.").

Therefore, while confirmed responses (primary endpoint) were only observed in patients with PROS caused by "frequent" PIK3CA mutations, additional clinical and nonclinical data suggest that patients with "less-frequent" PIK3CA mutations may still derive benefit from the treatment with alpelisib. These data support approval to a broader population of patients with PROS as proposed by the Applicant. Assessment across mutation subgroups in a future confirmatory trial will be included in a PMR (See Section 13 for details).

6.2.2.3. Outstanding Issues

Data and The Applicant's Position:
None.

The FDA's Assessment:
A PMC will be issued for dose optimization of alpelisib in pediatric patients 6 – 17 years old through evaluation of a higher dosage in this age group in a separate cohort of the ongoing EPIK-P2 trial. Refer to Section 13 for additional information.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data and The Applicant's Position:
All relevant information to support the clinical pharmacology profile of alpelisib was provided within the Piqray NDA.

The FDA's Assessment:
The FDA agrees.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. The PK of alpelisib have been characterized using both cancer patient studies and clinical pharmacology studies. Although no PK data are currently available in adult (≥18 years of age) or pediatric (2-17 years of age) patients with PROS, treatment with alpelisib in EPIK-P1 demonstrated clinically relevant, compelling, and sustained response with meaningful clinical benefit for PROS patients.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. The starting dose in pediatric patients 6 – 17 years old should be further evaluated for optimization. See Section 6.3.2.2 for detailed information on FDA considerations for the proposed pediatric dosage.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data and The Applicant's Position:

Yes. The proposed dose of alpelisib in pediatric patients (2-17 years) is 50 mg (one 50 mg tablet) taken orally once daily with food and in adult patients (≥ 18 years) is 250 mg (one 200 mg tablet and one 50 mg tablet) taken orally once daily with food. The available efficacy data from EPIK-P1 demonstrated clinically relevant, compelling, and sustained response with meaningful clinical benefit for patients (Section 8.1.2). Furthermore, no new safety concerns have been identified, as the majority of adverse events (AEs) are consistent with the known mechanism of action of the drug and compares favorably to the known safety profile in the oncology setting. Notably, the low frequency and generally mild severity of AEs suggest good tolerability and an acceptable and manageable safety profile (Section 8.2.5).

Dose modifications may be needed (e.g., for the management of adverse events (AEs), optimization of clinical responses, etc.), also considering that the treatment of patients with alpelisib is anticipated to be long-term. Based on data from EPIK-P1, 10/28 (35.7%) pediatric patients ≥ 6 years of age, had at least one dose increase of alpelisib from their respective starting doses and 4/18 (22.2%) of adult patients had at least one dose reduction [EPIK-P1-CSR-Table 10-26]. As such, Novartis is seeking approval of the 125 mg film-coated tablets to facilitate dose modifications and provide convenience for the patients.

The FDA's Assessment:

The FDA agrees with the proposed dosing regimen in adult patients with PROS. However, the recommended dosage in pediatrics is based on clinical experience in a compassionate use

program and has not been adequately justified with supporting data from a clinical pharmacology perspective. A dose optimization study should be conducted as a PMC based on the following considerations:

1. The pediatric dose is 1/5 of the adult dose with predicted exposure of <1/3 of the adult's exposure (see Table 6 below);
2. The response rate in pediatrics is numerically lower than adults (30% [95% CI: 13%-53%] vs 56% [95% CI: 21%-86%]) (see Table 7 below);
3. Forty-six percent of pediatric patients 6-17 years old had one or more dose escalation;
4. Among pediatric patients 6-11 years, response rate was 14%, and these patients had the highest median baseline target lesion volume compared to the other pediatric subgroups;
5. Subject level analysis identified limited volumetric response of the target lesion at 50 mg dose in some individuals with: 1) large baseline lesion burden (target lesion volume over 1000 mL), and 2) non-CLOVES subtype or less-frequent PIK3CA mutations (see Figure 1 below).

The analyses described in the considerations noted above and the referenced Figure are limited by the small sample size across and within subgroups, and are considered exploratory.

Table 6: Predicted AUC0-24h at steady-state in pediatrics following 50 mg alpelisib dose based on adult population PK model

Age (years)	Male		Female		Mean AUC (µg*hr/mL)
	Weight (kg)	AUC (µg*hr/mL)	Weight (kg)	AUC (µg*hr/mL)	
2	12.7	5.1	12.1	6.9	6.0
3	14.4	4.9	13.9	6.6	5.8
4	16.3	4.7	15.9	6.4	5.6
5	18.5	4.5	18.0	6.1	5.3
6	20.8	4.4	20.3	5.9	5.2
7	23.2	4.2	22.9	5.7	5.0
8	25.8	4.1	25.8	5.5	4.8
9	28.7	4.0	29.1	5.3	4.7
10	32.1	3.9	33.1	5.1	4.5
11	36.1	3.7	37.4	5.0	4.4
12	40.7	3.6	41.8	4.8	4.2
13	45.8	3.5	46.0	4.7	4.1
14	51.2	3.4	49.5	4.6	4.0
15	56.5	3.3	52.1	4.5	3.9
16	61.1	3.2	53.9	4.5	3.9
17	64.7	3.2	55.2	4.5	3.9

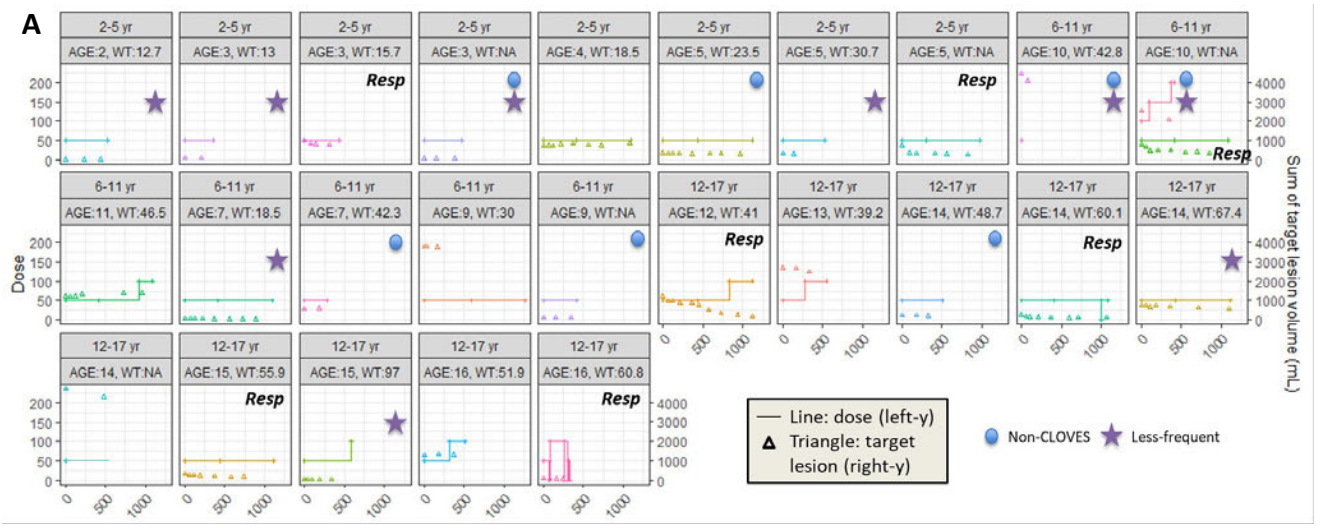
Source: The Applicant's population PK report for simulations of pediatric dosing regimen (Table 7-1).

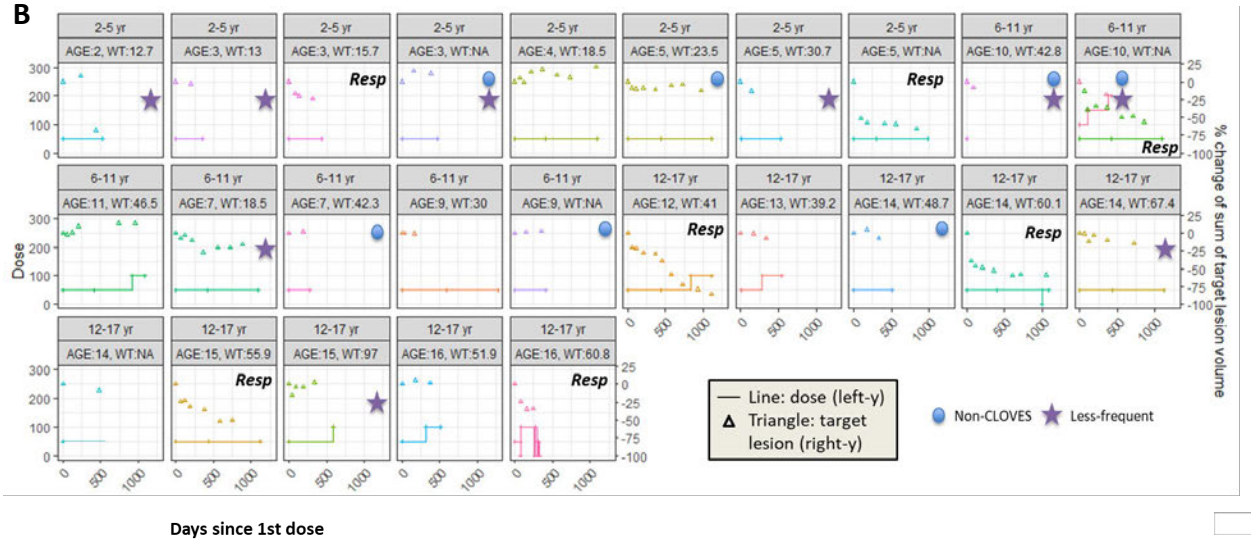
Table 7: Radiological response by age group in efficacy population with baseline and week 24 radiological evaluation

	2-5 years N=7	6-11 years N=7	12-17 years N=9	Pediatrics N=23	Adults N=9
Response rate, n (%) [95% CI]	2 (29%) [3.7, 71]	1 (14%) [0.4, 58]	4 (44%) [14, 79]	7 (30%) [13, 53]	5 (56%) [21, 86]
Duration of response, median in months (range)	14 (6-21)	22 (22-22)	23 (3-30)	21 (6-30)	0.9 (0.03-43)[#]
Percentage change in target lesion on Week 24*, median (range)	-9% (-57%-15%)	-0.5% (-34%-9%)	-4% (-49%-5%)	-4% (-57%-15%)	-21% (-46%-1%)
Sum of baseline target lesion volume, median in mL (range)*	333 (3-1000)	993 (50-4453)	531 (15-4719)	644 (3-4719)	2106 (17-6942

*Source: Excerpted from CSR of EPIK-P1 (Table 10-9, Table 10-14, Table 14.2-3.1). *The subjects of the full study population were included for summary. Full study population includes total of 57 subjects. However, baseline and Week 24 target lesion were only reported in 37 and 31 subjects, respectively. [#]Two adult subjects did not have adequate assessment past Week 24.*

Figure 1: Dose and lesion burden over time in pediatric patients overlaid with PROS subtype and mutations





Source: Reviewer's analysis of pediatric subjects in efficacy population (n=26). (A) Sum of target lesion volume; (B) % Change of sum of target lesion volume. Each square represents the unique record(s) by age group and weight (WT). NA indicates weight not available.

Considering that serious adverse effects (SAEs) were not found to be associated with doses higher than 50 mg in pediatrics in EPIK-P1, the FDA advised including a higher starting dose cohort (e.g., 125 mg) for patients 6-17 years old in the ongoing EPIK-P2 trial to evaluate potential additional clinical benefits at an earlier time in non-responders and in certain patients who are not likely to have adequate volumetric response at the current 50 mg dose. The FDA also considered recommending increasing the dose cap from the proposed 125 mg to 250 mg in pediatrics 12 years and older to potentially maximize the efficacy. However, FDA finds the Applicant's proposed pediatric dosage acceptable as there were no pediatric patients in this age cohort who dose escalated to 250 mg in EPIK-P1.

Additionally, the FDA considered recommending shortening the time interval from 24 weeks to 12 weeks for dose escalation based on data from the original compassionate use program, which showed that clinical response could be observed by Day 90 of alpelisib treatment for all 17 patients enrolled in the program. However, the FDA finds the Applicant's proposed dose escalation schedule acceptable as there was insufficient data regarding objective responses at week 12 in the EPIK-P1 trial to determine if clinical response can be observed in EPIK-P1 at week 12. Additional dose optimization will occur in the EPIK-P2 trial; in particular, a higher starting dose will be assessed for patients 6 – 17 years of age as part of a PMC. Refer to Section 13 for details regarding the PMC.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data and The Applicant's Position:
No alternative dosing regimen is required based on the intrinsic patient factors. The effect of intrinsic and extrinsic factors on alpelisib PK were thoroughly characterized in previous studies in healthy adult volunteers and in adult patients with advanced solid tumors, and is reflected in the approved label for breast cancer indication (Piqray USPI) (including human absorption, distribution, metabolism, elimination (ADME), food effect, hepatic impairment and drug-drug interaction studies). The clinical efficacy and safety results support the proposed dose regimen for patients with PROS. In addition, no PK sampling was conducted in the compassionate use programs in PROS patients 2 years and older, therefore no additional PK data of alpelisib in the target patient population are currently available.

The FDA's Assessment:

The FDA agrees with the Applicant's position that no additional data pertinent to dosing for subpopulations based on intrinsic factors has been provided. Dosing in pediatric patients 2 – 17 years old is reviewed in Section 6.2.2.1 and Section 6.3.2.2.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data and The Applicant's Position:
Information pertaining to the clinically relevant food-drug and drug-drug interactions were previously submitted in within the Piqray NDA.
In addition, the substrate specificity of alpelisib on additional transporter were studied [Non Clinical Overview Addendum 1] [DMPK R2000201], and it was demonstrated that alpelisib is not a substrate of BSEP, MRP2 or MATE1.

The FDA's Assessment:
The FDA agrees with the Applicant's position on clinically relevant food-drug and drug-drug interactions that have been previously submitted with the Piqray NDA.

The FDA also agrees with the Applicant's assessment that alpelisib is not a substrate of BSEP, MRP2, or MATE1. In Study DMPK R2000201, the ATP-dependent accumulation of alpelisib was tested at eight concentrations (0.25 ± reference inhibitor, 0.5, 1, 2.5, 5, 10, 25 and 50 µM) in BSEP- and MRP2-expressing and control vessels. Additionally, the accumulation of alpelisib was also tested at eight concentrations in MATE1-expressing and control cells in the presence of a reference inhibitor. See Table 8 for a summary of results.

Table 8. Summary of results from preclinical Study DMPK R2000201

Transporter assay	Maximum fold accumulation	Substrate*
BSEP VT	<2 (1.24) at 1 µM	Not a substrate
MRP2 VT	<2 (1.75) at 0.5 µM	Not a substrate
MATE1 UPT	<2 (1.05) at 2.5 µM	Not a substrate

VT: vesicular transport assay, UPT: uptake transporter assay

*If the fold accumulation value is > 2 and can be inhibited with at least 50% by a known inhibitor of the transporter the TA can be considered a substrate of the respective transporter.

Source: Contract Research Report for Study DMPK R2000201, pg 8.

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Lingshan Wang
Primary Reviewer

Hong Zhao
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 9: Listing of clinical trials relevant to this Type 10 NDA

Trial Identity.	NCT no	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study population	No. of Centers and Countries
Pivotal study to support efficacy and safety								
CBYL719F12002 (EPIK-P1)	NCT04285723	Site-based retrospective chart review of adult and pediatric patients ≥ 2 years of age with severe or life-threatening PROS who have received alpelisib as part of a compassionate use program (i.e. patients were treated under the ATU in France or the MAP outside of France). This study abstracted data from all eligible patients at	**Pediatric patients** (2 to 17 years): alpelisib 50 mg/daily orally **Adult patients** (≥18 years): alpelisib 250 mg once daily orally	**Primary**: • Proportion of patients with response at Week 24 or 6 months (+/- 4 weeks)[1] **Secondary**: • Changes in the sum of measurable target lesion (1 to 3 lesions) volume over time. • Changes in the sum of all measurable (target and non-target) lesion volume over time. • Changes in the sum of all	Treatment continued as long as clinical benefit was observed or until unacceptable toxicity occurred.	58 (one patient withdrew consent and as a result, 57 patients were included in the Full Study Population). Out of 57 patients, 39 were pediatric (≥ 2 to 17 years old) and 18 were adult (≥ 18 years old) patients	Adult or pediatric patients of ≥ 2 of age with a physician confirmed /documented diagnosis of PROS, with documented evidence of a mutation in the PIK3CA gene were enrolled.	7 sites in 5 countries

Trial Identity.	NCT no	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study population	No. of Centers and Countries
		all participating sites that had been previously recorded in the medical charts to assess the efficacy and safety of alpelisib for the treatment of the heterogeneous manifestations of PROS		measurable non-target lesion volume over time. • Duration of response. • Changes in type of medication and non-drug therapies over time. • Changes in PROS symptoms and complications over time. • Changes in functional status (e.g. work/school/preschool attendance. Mobility) over time • Changes in Healthcare resource use (HRU). • Changes in clinical assessments such as laboratory evaluation, vital signs and physical				

Trial Identity.	NCT no	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study population	No. of Centers and Countries
				findings over time. • Safety and tolerability of alpelisib				
Studies to support safety								
CBYL719X2101 (X2101)	NCT01928459	Phase IA, multicenter, open label dose escalation study in adult patients with advanced solid malignancies, whose tumors had an alteration of the PIK3CA gene	Alpelisib p.o. QD : 30, 60, 90, 180, 270, 300, 350, 400, 450 mg Alpelisib p.o. BID: 120, 150, 200 mg	**Primary**: MTD of alpelisib as single agent and in combination with fulvestrant **Secondary**: ORR, DCR, PK profile of alpelisib	No specific treatment duration, patients were treated until they met the criteria for study discontinuation (e.g. disease progression, unacceptable toxicity, patient withdrawal, investigator's discretion)	134		11 centers in 5 countries
CBYL719X1101 (X1101)	NCT01387321	Phase I, open label, multicenter study in adult Japanese patients with advanced solid malignancies and documented genetic alteration of the PIK3CA gene	Alpelisib p.o. QD escalation part: 90, 180, 270, 350, 400 mg Alpelisib p.o. QD expansion part: 350 mg	**Primary**: MTD of BYL719 as single agent in subjects with advanced solid malignancies **Secondary**: Safety and tolerability of BYL719, PK profile of BYL719 after single and multiple	No specific treatment duration, patients were treated until they met the criteria for study discontinuation (e.g. disease progression,	33		4 centers in 1 country (Japan)

Trial Identity.	NCT no	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study population	No. of Centers and Countries
				administrations, and ORR	unacceptable toxicity, patient withdrawal, investigator's discretion)			
[1]Definition of response provided below under the Study Endpoints section. ORR: overall response rate, DCR: Disease control rate, PK: Pharmacokinetics, MTD: Maximum tolerated dose, p.o. BID: Orally twice a day								

The Applicant's Position:

The results from the pivotal study EPIK-P1 form the basis of a Type 10 NDA submission in support of an indication for alpelisib for the treatment of adult and pediatric patients ≥2 years of age with PROS. Supportive evidence of safety is provided from 167 patients exposed to single-agent alpelisib in dose-finding Studies CBYL719X2101 and CBYL719X1101 in adult patients with advanced solid malignancies, whose tumors had an alteration of the PIK3CA gene (Table 8).

The FDA's Assessment:

In general, the FDA agrees with the Applicant's descriptions of the studies as outlined in Table 9; however, EPIK-P1 is a single-arm clinical study that included data from patients enrolled in an MAP/expanded access program under a prospectively designed clinical protocol "guidance document" for treatment and monitoring. The study did not enroll all eligible patients with PROS who had been treated via expanded access. The Applicant did conduct an initial site feasibility assessment and contacted 11 sites at which patients with PROS were receiving alpelisib for treatment. Although all 11 sites were reported to have expressed interest in participating in EPIK-P1, ultimately seven sites were selected for participation across France, Australia, Ireland, Spain and the US. Per the Applicant, the four remaining sites (representing four patients in total) were not selected as they could not meet projected study timelines for various reasons (e.g., historically lengthy [greater than 3 months] process for ethics committee or institutional review board [IRB] approval, unresponsiveness, and/or long contracting timelines). Additionally, although the regimen of alpelisib described in Table 9 corresponds to dosing recommended in the Applicant's protocol for the Managed Access Program, pediatric patients in EPIK-P1 were treated with varying doses at the discretion of each patient's physician (administered doses ranged from 50 mg to 250 mg).

In EPIK-P1, patient-level data were retrospectively abstracted from medical records of consenting eligible patients with PROS at participating clinical sites by trained personnel using an electronic data capture (EDC) platform that is compliant with 21 CFR Part 11 to complete electronic case report forms (eCRF) and compile individual patient narratives. All data available for each patient and study variable were collected during the pre-index and the study period (extending from index date to data cut-off). If a patient discontinued alpelisib prior to the data cut-off, only data reported up to 30 days after the last date of study treatment were abstracted and entered into the database. Analyses were performed by the Applicant or designated contract research organization (CRO) using SAS version 9.4 or later software to generate tables, figures and listings. Collected data was converted to conform to CDISC data standard for electronic submissions.

The primary efficacy results supporting the NDA are from the efficacy population, a subset of 37 patients from EPIK-P1. The primary safety results supporting the NDA are from the overall safety population, consisting of 57 patients enrolled in EPIK-P1. Supportive safety data in the NDA comes from results of studies X2101 and X1101, which are listed in the "Studies to Support Safety" section of Table 9.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

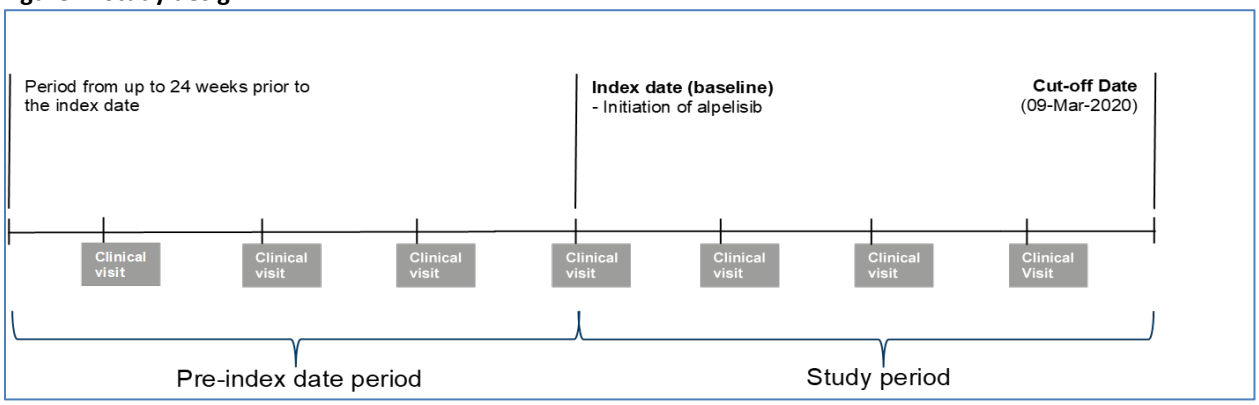
8.1.1. EPIK-P1

Trial Design

The Applicant's Description:

EPIK-P1 was a retrospective chart review of pediatric and adult male and female patients with severe or life-threatening conditions of PROS treated with alpelisib as part of a compassionate use program (i.e., under the ATU in France and under the MAP in Australia, Ireland, Spain and the US). This study abstracted data from eligible patients at participating sites in EPIK-P1 and pooled longitudinal information that had been previously recorded in their medical charts, in order to assess the efficacy and safety of alpelisib for the treatment of the heterogeneous manifestations of PROS. A schematic representation of the study design is presented in Figure 2.

Figure 2: Study design



Available information from all clinic visits including the pre-index date period (from up to 24 weeks prior to the index date through to the day prior to the index date), the index date (date of alpelisib treatment initiation), and the study period (period from the index date up to the data cut-off of 09-Mar-2020) were abstracted. Additionally, available prior PROS medications and PROS related surgical/vascular interventions were collected since diagnosis. If a patient discontinued treatment prior to the cut-off date, data reported up to 30 days after the last date of study treatment were abstracted.

To mitigate potential physician bias related to lesion assessment, the lesions for the analyses of the study endpoints were independently selected by a radiologist at the independent central radiology review (ICRR) using the pre-index date images and clinical information regarding symptoms related to lesions as provided by the treating physician. All available MRI scans, CT

scans, and photographs were to be submitted to the independent central radiology review and were processed into the imaging repository as specified by the imaging charter. Radiological response and non-response were defined based on the change in the sum of the target lesions volume, as assessed by MRI/CT imaging by ICRR. One to three target lesions were chosen for volumetric measurement at the index date (baseline) of the study.

The cut-off date (09-Mar-2020) was selected to minimize the impact of the COVID-19 pandemic on data integrity and was discussed with and agreed upon by the FDA. Eligible patients were those who initiated alpelisib on or before 23-Sep-2019. At the time of the cut-off, the COVID-19 pandemic did not have major consequences on the regular management of the patients in the countries participating in the ATU and the MAP.

Trial location: 7 sites across 5 countries.

Inclusion criteria: Eligible patients (≥ 2 years of age) who had clinical manifestations of PROS that were assessed by the treating physician as severe or life-threatening and necessitating treatment, and had documented evidence of mutation in the PIK3CA gene as determined by a local laboratory were enrolled.
Exclusion criteria: None.

Dose selection: The doses recommended for patients treated in EPIK-P1 were based on those empirically selected in the initial compassionate use program and supported by data in Venot et al 2018.

Study treatment: All patients were treated with alpelisib based on physician judgement in the context of the compassionate use program. For pediatric patients (2-17 years), the recommended dose was 50 mg once daily with food. For adult patients (≥ 18 years), the recommended dose was 250 mg taken orally once daily with food.

Dose modification, dose discontinuation: For pediatric patients unable to tolerate the administered dose, dose interruption or discontinuation was recommended. For adult patients unable to tolerate the administered dose, dose adjustment, dose interruption, or dose discontinuation were recommended. Based on data summarized in Table 30 (Section of Dose Interruption/Reduction Due to Adverse Effects), these recommendations seem appropriate.

Administrative structure: Trial oversight was managed by a Steering Committee, consisting of selected investigators and Sponsor representatives, ensuring conduct of the study in accordance with the protocol. (b) (4) were the other parties responsible for the conduct of the study.

Procedures and schedule: All efficacy and safety variables were assessed during the pre-index period and during the study period until the cut-off date (09-Mar-2020). For reporting purposes, key time-points following the index date are defined in Table 10. All time-points available for each patient up to and including the cut-off date were reported.

Table 10: Time windows for post-index date key time-point

Key time-points	Allowed windows
4 weeks	Up to 10 weeks
12 weeks	[10 to 20 weeks[
24 weeks[1]	[20 to 32 weeks[
36 weeks	[32 to 40 weeks[
52 weeks	[40 to 58 weeks[
End of study	4 weeks prior to and up to min(study treatment discontinuation + 30 days, cut-off date)

[1]24 weeks or 6 months (+/- 4 weeks)

Concurrent medications: Details of concomitant medication and non drug therapies are described under the secondary objective of 'Changes in type of medication and non-drug therapies over time' in the section below.

Patient completion, discontinuation, or withdrawal: Data from eligible patients, i.e., those who initiated alpelisib on or before 23-Sep-2019 were collected. If a subject discontinued treatment prior to 09-March 2020, data reported up to 30 days after the last date of study treatment were abstracted and entered into the database.

The FDA's Assessment: Overall, the FDA agrees with the Applicant's description of EPIK-P1, except that the FDA considers EPIK-P1 a single-arm clinical study, not a trial. EPIK-P1 was a single-arm clinical study that enrolled eligible patients from those participating in the compassionate use program referred to as ATU (Temporary Authorization for Use) in France and the Applicant's global Managed Access Program (MAP) for alpelisib for the treatment of PROS ("MAP Cohort Treatment Plan CBYL719F12001M to provide access to Alpelisib [BYl719] for patients with PROS"), additional details regarding these expanded access programs derived from the Applicant's treatment plan are discussed below.

The major eligibility criteria implemented are listed here:

MAP Eligibility Criteria

1. An independent request should be received from the physician or other Health Care Professional (HCP), where regulations allow
2. The patient to be treated has a serious or life threatening disease or condition, and no comparable or satisfactory alternative therapy is available to monitor or treat the disease or condition

3. The patient is not eligible or able to enroll in a clinical trial
4. There is a potential patient benefit to justify the potential risk of the treatment use, and the potential risk is not unreasonable in the context of the disease or condition to be treated
5. The patient must meet any other important medical criteria established by the medical experts working on the product development program
6. Provision of the investigational product will not interfere with the initiation, conduct or completion of the Applicant's clinical trial or overall development program
7. Such access provision as described above is allowed as per local laws and regulations

Medical Inclusion Criteria for MAP Patients

Patients eligible for inclusion in this treatment plan were required to meet all of the following criteria:

1. Adult or pediatric patients ≥ 2 years of age, with a diagnosis of PROS preferably with evidence of a mutation in the PIK3CA gene
2. The treating physician has determined that the patient's condition is severe or life threatening, treatment is necessary and there are no other feasible alternatives for the patient
3. Confirmed adequate bone marrow function

Dose modification guidelines described in the expanded access program treatment plan are summarized as follows:

- For pediatric patients unable to tolerate the administered dose, dose interruption or discontinuation was recommended.
- For adult patients unable to tolerate the administered dose, dose adjustment, dose interruption, or dose discontinuation were recommended. In general, two dose reductions were permitted (starting dose: 250 mg daily; dose level -1: 200 mg daily, dose level -2: 125 mg daily) with the exception of pancreatitis, for which only one dose reduction was allowed.
- Patients who experience adverse events of Grade 3 or higher severity (except hyperglycemia) or do not tolerate the dosing schedule recommended in the treatment plan should permanently discontinue treatment.
- Guidelines for suggested management, including interruption, dose modification and re-initiation of alpelisib treatment, of selected toxicities (skin toxicity, hyperglycemia, pneumonitis, diarrhea, stomatitis/oral mucositis, amylase and lipase elevation, hypersensitivity, and other adverse reactions) and general recommendations for management of "other adverse reactions" were also provided in the protocol.

The treatment plan stated that patients must be informed to notify their physician about any

medications and significant non-drug therapies (including physical therapy and herbal/natural medication) administered during treatment and that these interventions should be noted in the patient's record. The expanded access program treatment plan also detailed information regarding permitted and prohibited concomitant medications and non-drug therapies.

A recommended visit evaluation schedule (Figure 3) was also included in the treatment plan for the expanded access program. Treating physicians were advised to monitor patient safety by assessing physical examination, hematology and chemistry laboratory studies, and any other pertinent testing required as part of the safety profile of alpelisib. Notably, periodic imaging evaluations were not required or recommended in the assessment schedule below.

Figure 3: Schedule of Assessments from MAP Cohort Treatment Plan CBYL719F12001M

Activity / Test	Baseline (prior to drug start)	Every 3 to 4 weeks during the first 3 months and thereafter/or as clinically indicated	End of Treatment (EOT)
Informed Consent	X		
Medical History	X		
Physical Exam	X	X	X
Vital signs	X	X	X
Pregnancy Test (if appropriate)	X	X	X
Laboratory Test			
Hematology Tests			
White Blood Count with Differential	X	X	X
Hemoglobin	X	X	X
Platelets	X	X	X
Chemistry Tests			
Potassium	X	as clinically indicated	X
Sodium	X	as clinically indicated	X
Calcium	X	as clinically indicated	X
Magnesium	X	as clinically indicated	X
Chloride	X	as clinically indicated	X
Inorganic phosphorus	X	as clinically indicated	X
Alanine aminotransferase (ALT) (SGPT)	X	as clinically indicated	X
Aspartate aminotransferase (AST) (SGOT)	X	as clinically indicated	X
Alkaline phosphatase	X	as clinically	X
Total bilirubin	X	as clinically indicated	X
LDH	X	as clinically indicated	X
Gamma GT	X	as clinically indicated	X
Creatinine	X	as clinically indicated	X
Urea or blood urea nitrogen (BUN)	X	as clinically indicated	X
Lipase	X	as clinically indicated	X
Albumin	X	as clinically indicated	X
Uric acid	X	as clinically indicated	X
Fasting plasma glucose	X	X	X
Coagulation (PTT & PT or INR)	X	as clinically indicated	
Lipase	X	as clinically indicated	X
Albumin	X	as clinically indicated	X
Uric acid	X	as clinically indicated	X
Fasting plasma glucose	X	X	X
Coagulation (PTT & PT or INR)	X	as clinically indicated	
C-peptide	X	as clinically indicated	X
Glycosylated hemoglobin (HbA1c)	X	X (every 3 months)	X (and 3 months after EoT)
Safety Review			
Adverse events (AEs)	Report Serious AEs Immediately Collect all AEs and report as specified (refer to Section 8)		
Concomitant Medications	Continually review to avoid prohibited concomitant medications		

Collection of adverse events was required at every visit. Reporting of safety information to the local health authority and/or to the ethics committee/IRB followed local laws and regulations. Further, treating physicians were required to report any serious adverse events and safety report submitted to the ethics committee/IRB to the Applicant's local patient safety

department in the country.

Finally, the Applicant's treatment plan for alpelisib for patients with PROS stipulated that some information (including patient demographics, disease characteristics at baseline, and first and last treatment date) will be collected at the time of patient request submission to allow the Applicant to approve inclusion of a patient in the MAP cohort and at time of resupply, if applicable, to understand how the patient is deriving benefit from alpelisib.

Study Endpoints

The Applicant's Description:

The primary endpoint was response (yes/no) at Week 24 or 6 months (+/- 4 weeks) by the ICRR. A response was defined by achieving at least 20% reduction from the index date in the sum of measurable target lesion volume (1 to 3 lesions), provided that none of the individual target lesions have at least ≥ 20% increase from the index date to Week 24 or 6 months (+/- 4 weeks) and in absence of progression of non-target lesions and without new lesions. Patients who permanently discontinued alpelisib prior to 24 weeks of treatment, patients who required surgery as rescue therapy between the index date and 24 weeks of treatment and patients with MRI scan performed at Week 24 or 6 months (+/- 4 weeks) for which the volumetric measurement of the selected target lesions was not calculated (i.e. unknown) were defined as non-responders.

The primary endpoint for this study, which was assessed via ICRR, was selected as it is an objective and quantitative outcome measure associated with manifestations of PROS that is observable in a significant proportion of the heterogeneous patient population eligible for inclusion. In addition, reduction of at least 20% in the volume of the most clinically relevant PROS target lesion was associated with clinical benefit in patients with this condition as documented in the Venot et al. 2018 publication.

The secondary endpoints for this study were selected to assess the clinical benefit of alpelisib and to supplement information obtained from the analysis of the primary endpoint. These, included percent change in the sum of measurable target lesion (1 to 3 lesions) volume over time, the percent change in the sum of all measurable (target and non-target) lesion volume over time, the percent change in the sum of all measurable non-target lesion volume over time and duration of response (defined as the time from first documented response, to the date of the first documented disease progression or death due to any cause). There are no benchmarks for mid-term and long term effects of medical treatments in PROS. These assessments of the target and non-target lesions over time provide objective and robust evidence of the drug's early and sustained effect on the local overgrowth. At the Week 52 time point, the percentage of patients with response was reported for exploratory purposes.

Other secondary endpoints included change in PROS symptoms and complications over time,

change in functional status over time, change in clinical and laboratory results over time, change in the type of medications and non-drug therapies used for the management of PROS complications over time, change in health resource utilization use (HRU) over time, as well as safety and tolerability of alpelisib. These endpoints support the clinical risk/benefit assessment of alpelisib and supplement information obtained from the analysis of the primary endpoint.

The list of variables associated with each endpoint was developed based on a pre-study feasibility assessment conducted with the participating sites. Based on this feasibility assessment, the variables listed were expected to be available for most patients across most sites. Efficacy assessments selected for EPIK-P1, were deemed appropriate for evaluating the efficacy of alpelisib in PROS and were discussed with and agreed upon by the FDA.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the endpoint. However, the FDA considers confirmed response rate (i.e., responses that have been confirmed by a subsequent imaging assessment) to be the relevant regulatory endpoint and an endpoint reasonably likely to predict clinical benefit. Further FDA assessment of observed results will be based on confirmed response rate.

In addition, as noted by the Applicant, the use of volumetric reduction in target lesion(s) to determine response rate in EPIK-P1 was considered acceptable by the FDA. For lesions that are complex and irregularly shaped with possibly indolent growth patterns, linear measurements may not be practical or meaningful for disease evaluation, in which case alternative methods for response assessment may be better suited to evaluate progression. For example, the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria, which are based on volumetric measurements by MRI, were used to support the FDA approval of selumetinib for the treatment of pediatric patients with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (Dombi et al., 2013). Although tissue overgrowths ("lesions") in patients with PROS are not tumors, lesions observed in patients with PROS are similar to plexiform neurofibromas in that they are atypical and generally slowly progressive. As such, the volumetric-based response criteria proposed by the Applicant to support the primary endpoint in EPIK-P1 were determined to be appropriate.

Statistical Analysis Plan and Amendments
The Applicant's Description:
The SAP was finalized prior to any data abstraction. Prior to the database lock, the SAP was amended 3 times. Key changes included:

- Amendment 1 released on 26-May- 2020: Primary analysis was revised to be based on the complete case analysis (analysis on all patients in the efficacy population without missing response at week 24) (details provided in the protocol amendment section below)

- Amendment 2 released on 07-Aug-2020: Clarifications and corrections were made around time windows (key post index date time points for reporting endpoint over time and subgroup analyses for the primary endpoint)
- Amendment 3 released on 19-May-2021: Extend the time window for the baseline imaging scans to include imaging scans performed up to 24 weeks prior to index date to allow flexibility, considering the retrospective nature of the study. Replaced Week 24 (+/- 4 weeks) with Week 24 or 6 months (+/- 4 weeks) to be consistent with clinical practice.

Efficacy analysis: The efficacy population included patients with at least one target lesion and with an imaging scan performed on the index date (or up to 24 weeks prior to the index date) for at least one target lesion. The primary analysis was performed on all patients in the efficacy population without missing response at week 24 (complete case analysis). The primary analysis for this study was descriptive (estimation based), and therefore no hypothesis testing was conducted. Categorical and binary variables were summarized using frequency counts and percentages. The Clopper-Pearson exact method was used to estimate two-sided 95% CIs for binary data.

Subgroup analyses for primary endpoint were conducted based on age, sex, mutation type, lesion type, PROS subtype, prior treatment status, body weight in pediatric patients, and pre-index diabetic status. Sensitivity analyses were performed to assess the robustness of the primary efficacy results.

All the secondary efficacy endpoints were reported using the Full study population (all patients that satisfied the study inclusion criteria). To analyze data over time, all available data were used. No imputation methods were performed. The secondary analyses for this study were descriptive and therefore no hypothesis testing was performed.

Safety analysis: All safety analyses were based on the Full study population. The assessment of safety and tolerability was based mainly on the type, frequency, seriousness, and severity criteria and causality assessments of treatment-emergent adverse events, changes in laboratory variables (with particular attention to grade 3-4 abnormalities).

Handling of missing data: As EPIK-P1 was a retrospective study, information was not always systematically collected at each time-point of interest, resulting in missing data. All patients in the efficacy population without a missing response at week 24 were used for the primary analysis of the primary endpoint (complete case analysis).
The completeness of the response variable was enumerated by reporting the following:

- Reasons for missing response at week 24 or 6 months (+/- 4 weeks), including missing imaging scans, as available were reported.
- Differences in the patient population with regard to demographic and clinical

characteristics (e.g., age, PROS sub-type) were reported in a table for patients with and without 24 weeks or 6 months (+/- 4 weeks) assessments.

- Patients with missing responses at 24 weeks or 6 months (+/- 4 weeks) were considered as non-responders for sensitivity analysis 3 of the primary end point.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's description of the SAP. However, the FDA does not agree with exclusion of patients with a missing response assessment at Week 24 from the primary efficacy population; instead, the efficacy analysis should be performed on all patients with at least one target lesion and with an imaging scan performed on the index date (or up to 24 weeks prior to the index date) for at least one target lesion, even if there was a missing response assessment at Week 24. Patients with a missing response assessment at Week 24 should be considered non-responders.

Protocol Amendments

The Applicant's Description:

The study protocol was amended once; no patients were enrolled in EPIK-P1 prior to the protocol amendment. The key changes implemented in the amendment are described below:

- The cut-off date definition was changed to avoid missing data due to the COVID-19 pandemic.
- Following discussion with FDA, the primary analysis was modified at the Agency's request. In the original protocol, the primary analysis applied imputation of the missing volumetric assessments for target lesions at Week 24 (± 4 weeks), while in the amended protocol a complete case analysis is utilized. The complete case analysis was performed based on patients without missing responses at Week 24. The analysis using imputed data was performed as a sensitivity analysis (instead of as the primary analysis).
- Duration of response was added as a secondary objective.

The amendment to the EPIK-P1 protocol did not have an impact of the integrity of the trial or the interpretation of the results.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the EPIK-P1 protocol amendment.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data and The Applicant's Position:
EPIK-P1 was designed, implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the reporting of observational studies in epidemiology) guidelines (Von Elm et al. 2007), and with the ethical principles laid down in the Declaration of Helsinki. Studies EPIK-P1, X2101 and X1101 were conducted in compliance with current Good Clinical Practices. All studies were closely monitored by Novartis personnel or a contract organization for compliance to the protocol, Novartis standard operating procedures and applicable regulatory guidance.

Informed consent, if required by local laws, was obtained prior to data abstraction, for eligible subjects interested in participating in the study.

The FDA's Assessment:
The FDA acknowledges the Applicant's statement of compliance with GPP. Additionally, in Module 1.3 (*Administrative Information*), the Applicant notes that their "data management [team] and a designated contract research organization (CRO) assured database quality processes were followed including review of the data entered in the electronic case report forms (eCRFs) by investigational staff for completeness and accuracy in accordance with the data management plan. To ensure the accuracy and integrity of the data collected for EPIK-P1, [the Applicant] implemented a monitoring plan in accordance with their standard operating procedures (SOPs). The monitoring plan describes the monitoring methods, responsibilities and requirements to ensure data integrity, GCP compliance, and quality with a risk-based approach."

Financial Disclosure

Data and The Applicant's Position:
Details of financial disclosure are presented in Appendix 19.2.

The FDA's Assessment:
Financial disclosures were provided by the Applicant and are summarized in Section 19.2. In the FDA's assessment, the steps taken to minimize bias of clinical trial results by any of the disclosed arrangements or interests were sufficient.

Patient Disposition

Data:

Table 11: Patient disposition by age category (Full study population)

Disposition Reason	Pediatric patients 2-5 years N=11 n (%)	6-11 years N=12 n (%)	12-17 years N=16 n (%)	< 18 years N=39 n (%)	Adult patients ≥ 18 years N=18 n (%)	All patients N=57 n (%)
Patients treated	11 (100)	12 (100)	16 (100)	39 (100)	18 (100)	57 (100)
Treatment ongoing	11 (100)	11 (91.7)	14 (87.5)	36 (92.3)	16 (88.9)	52 (91.2)
Discontinued	0	1 (8.3)	2 (12.5)	3 (7.7)	2 (11.1)	5 (8.8)
Reason for discontinuation						
Subject decision	0	0	1 (6.3)	1 (2.6)	2 (11.1)	3 (5.3)
Physician decision	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
Other	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)
No efficiency	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)

Treatment ongoing at the time of data cut-off.
Source: EPIK-P1-CSR-Table 14.1-1.2

The Applicant's Position:

Overall, of the 58 patients enrolled in the study, 57 patients were included in the Full study population as one patient withdrew consent. The majority of patients continued to receive treatment as of the cut-off date (Table 10).

The FDA's Assessment:

The FDA agrees with the description of patient disposition of all patients who received any study drug and provided consent. The disposition of patients in the Efficacy analysis population is provided in Table 12.

Table 12: Patient disposition by age category (Efficacy Analysis population)

Disposition Reason	N=37 n (%)
Patients treated	57 (100)
Treatment ongoing	52 (91.2)
Discontinued	5 (8.8)
Reason for discontinuation	
Subject decision	3 (5.3)
Physician decision	1 (1.8)

Disposition Reason	N=37 n (%)
Other	1 (1.8)

Protocol Violations/Deviations

Data and The Applicant's Position:
Protocol deviations occurred in two patients (3.5%). Data entry for these two patients commenced prior to Ethics committee (EC) approval, signed agreement, Site Initiation Visit, and informed consent being obtained; this was considered as a GCP deviation. Of note, none of the data collected were used until all procedures described above were fulfilled and consent was obtained from these patients later in the course of study prior to any additional data abstraction. Since this was a retrospective, non-interventional study, the safety, the rights of the patients and data integrity were not impacted or compromised, and no procedure was performed to the patients, these deviations did not impact any study populations.

The FDA's Assessment:
The FDA agrees with the Applicant's description of protocol deviations. The FDA notes that protocol violations/deviations described do not refer to adherence to the expanded access treatment plan but rather to EPIK-P1. The protocol deviations described above do not affect interpretability of study results.

Table of Demographic Characteristics

Data:

Table 13: Demographics and clinical characteristics at index date by age category (Full study population)

Demographic variable	2-5 years N=11	6-11 years N=12	12-17 years N=16	Pediatric patients (<18 years) N=39	Adult patients (>=18 years) N=18	All patients N=57
Age (years)						
n	11	12	16	39	18	57
Mean (SD)	3.6 (1.21)	9.1 (1.44)	14.8 (1.57)	9.9 (4.84)	27.8 (8.34)	15.5 (10.39)
Median	3.0	9.0	15.0	10.0	25.5	14.0
Q1-Q3	3.0-5.0	8.0-10.0	14.0-16.0	5.0-14.0	22.0-32.0	9.0-22.0
Min-Max	2-5	7-11	12-17	2-17	18-50	2-50
Sex-n (%)						
Female	8 (72.7)	6 (50.0)	10 (62.5)	24 (61.5)	9 (50.0)	33 (57.9)
Male	3 (27.3)	6 (50.0)	6 (37.5)	15 (38.5)	9 (50.0)	24 (42.1)
Race-n (%)						

Demographic variable	2-5 years N=11	6-11 years N=12	12-17 years N=16	Pediatric patients (<18 years) N=39	Adult patients (>=18 years) N=18	All patients N=57
Not reported	10 (90.9)	9 (75.0)	13 (81.3)	32 (82.1)	18 (100)	50 (87.7)
White	1 (9.1)	3 (25.0)	3 (18.8)	7 (17.9)	0	7 (12.3)
Ethnicity-n (%)						
Not reported	5 (45.5)	6 (50.0)	10 (62.5)	21 (53.8)	14 (77.8)	35 (61.4)
Unknown	5 (45.5)	3 (25.0)	2 (12.5)	10 (25.6)	4 (22.2)	14 (24.6)
Not Hispanic or Latino	1 (9.1)	2 (16.7)	2 (12.5)	5 (12.8)	0	5 (8.8)
Hispanic or Latino	0	1 (8.3)	2 (12.5)	3 (7.7)	0	3 (5.3)
Body mass index (kg/m^2)						
n	8	7	11	26	8	34
Mean (SD)	16.84 (2.134)	20.76 (4.264)	21.98 (4.913)	20.07 (4.513)	24.32 (6.003)	21.07 (5.140)
Median	16.67	21.23	20.58	20.05	22.74	20.19
Q1-Q3	15.74-18.12	16.73-25.27	19.34-23.53	16.73-21.67	19.00-29.08	17.04-23.49
Min-Max	13.4-20.3	14.2-26.1	15.9-34.8	13.4-34.8	18.3-34.7	13.4-34.8
ECOG performance status-n (%)						
0	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)
2	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
3	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
Missing	11 (100)	11 (91.7)	14 (87.5)	36 (92.3)	18 (100)	54 (94.7)
Lansky-n (%)						
10-40	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)
40-50	3 (27.3)	1 (8.3)	1 (6.3)	5 (12.8)	0	5 (8.8)
60-70	3 (27.3)	1 (8.3)	5 (31.3)	9 (23.1)	0	9 (15.8)
80-90	2 (18.2)	5 (41.7)	0	7 (17.9)	0	7 (12.3)
100	0	0	2 (12.5)	2 (5.1)	0	2 (3.5)
Missing	3 (27.3)	4 (33.3)	8 (50.0)	15 (38.5)	18 (100)	33 (57.9)
Karnofsky-n (%)						
10-40	0	0	0	0	1 (5.6)	1 (1.8)
40-50	0	0	2 (12.5)	2 (5.1)	5 (27.8)	7 (12.3)
60-70	1 (9.1)	0	3 (18.8)	4 (10.3)	3 (16.7)	7 (12.3)
80-90	0	1 (8.3)	2 (12.5)	3 (7.7)	2 (11.1)	5 (8.8)
100	0	0	0	0	2 (11.1)	2 (3.5)
Missing	10 (90.9)	11 (91.7)	9 (56.3)	30 (76.9)	5 (27.8)	35 (61.4)

Source: EPIK-P1-CSR-Table 14.1-3.1

The Applicant's Position:

Patients were included across 7 sites in five countries (France (50 patients), Spain (three patients), US (two patients), Ireland (one patient), and Australia (one patient)). Forty-four of the total 57 patients (77.2%) were included at the Necker Hospital, Paris, France. Race and ethnicity were not reported for the majority of patients (50 patients, 87.7%), as these were not collected in the source document for most of the patients enrolled in France. The regional representation and demographics being contributed by the seven selected sites was anticipated to be representative of the overall PROS population (Table 12).

The FDA's Assessment:

In general, the FDA agrees with the description of the baseline demographic characteristics for the full study population. Of note, 88% of patients were treated in France (of 50 patients, 44 were treated at a single center) and race/ethnicity was not reported for the majority of study patients, largely due to local regulations that restrict the collection of such data. The FDA is requesting a postmarketing requirement for the conduct of a multiregional clinical trial to verify and describe the clinical benefit of alpelisib; the PMR states that the distribution of race and ethnicity in the patient population studied should be sufficiently reflective of the U.S. patient population to support generalizability of results to U.S. patients with PROS. Refer to Section 13 for details regarding the PMR.

However, the FDA considers the summary of demographic and clinical characteristics for the efficacy population to be more relevant for the purposes of the efficacy evaluation, as presented in Table 14.

Table 14: Demographics and clinical characteristics at index date by age category (Efficacy population)

	All Population N = 37 n (%)
Age	
Median (range)	14 (2-38)
Age 2-5	8 (22)
Age 6-11	8 (22)
Age 12-17	10 (27)
Adult (18+)	11 (30)
Sex	
Female	21 (57)
Male	16 (43)
Ethnicity	
Hispanic or Latino	1 (3)
Not Hispanic or Latino	4 (11)

	All Population N = 37 n (%)
Not reported	22 (59)
Unknown	10 (27)
Country	
France	33 (89)
Other (Australia, Spain, US, Ireland)	4 (11)
ECOG PS	
PS = 0	1 (3)
Missing	36 (97)
Lansky at baseline	
40-50	4 (11)
60-70	7 (19)
80-90	5 (14)
100	1 (3)
Missing	20 (54)
Karnofsky at baseline	
10-40	1 (3)
40-50	2 (5)
60-70	5 (14)
80-90	3 (8)
100	1 (3)
Missing	25 (68)
Mutation type	
Frequent	25 (68)
E542K[1]	9 (24)
H1047R[1]	6 (16)
H1047L[2]	2 (5)
E545K	4 (11)
C420R	5 (14)
N345K	2 (5)
T1025A	1 (2.7)
Less-frequent	12 (32)
E545A	1 (2.7)
E545G	1 (2.7)
E545K	4 (11)
Other[2]	7 (19)
PROS Subtypes	
CLOVES[3,4]	30 (81)

	All Population N = 37 n (%)
MCAP[3]	3 (8)
KTS	1 (2.7)
FIL	3 (8)
Other	2 (5)
Diabetic status at baseline	
Diabetic	1 (3)
Normal	26 (70)
Pre-diabetic	3 (8)
Unknown	7 (19)
Disease Status	
Congenital Overgrowth	34 (92)
Early Childhood-onset of Overgrowth	3 (8)
Previous PROS medication	
No	11 (30)
Yes	26 (70)
Prior use of sirolimus	
No	18 (49)
Yes	19 (51)
Prior use of taselisib	
No	32 (86)
Yes	5 (14)
Prior Surgery	
No	37 (100)
Mosaicism Proportion %	
>1%	33 (89)
Missing	4 (11)

[1]Patient (b) (6) had both E542K and H1047R mutation.
[2]Patient was originally classified as less frequent, but should be classified as H1047L type
[3]Two pa BJID (b) (6)) have both CLOVES and MCAP subtypes.
[4]All responders have CLOVES subtype.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 15: PROS disease history at the index date by age category (Full study population)

Disease history	2-5 years N=11	6-11 years N=12	12-17 years N=16	Pediatric patients (<18 years) N=39	Adult patients (>=18 years) N=18	All patients N=57
Time since confirmed diagnosis (years)						
Mean (SD)	3.6 (1.21)	8.8 (1.99)	14.1 (2.62)	9.5 (4.81)	27.8 (8.34)	15.3 (10.52)
Median	3.0	9.0	14.5	10.0	25.5	14.0
Min - Max	2 – 5	4 - 11	7 - 17	2 - 17	18 - 50	2 - 50
Onset of disease-n (%)						
Congenital overgrowth	11 (100)	11 (91.7)	16 (100)	38 (97.4)	15 (83.3)	53 (93.0)
Early childhood-onset of overgrowth	0	1 (8.3)	0	1 (2.6)	3 (16.7)	4 (7.0)
Overgrowth type-n (%)						
Mosaic distribution	10 (90.9)	12 (100)	16 (100)	38 (97.4)	18 (100)	56 (98.2)
Sporadic occurrence	1 (9.1)	0	0	1 (2.6)	0	1 (1.8)
PROS subtype-n (%)						
CLOVES	7 (63.6)	7 (58.3)	13 (81.3)	27 (69.2)	15 (83.3)	42 (73.7)
MCAP	4 (36.4)	2 (16.7)	2 (12.5)	8 (20.5)	0	8 (14.0)
KTS	0	1 (8.3)	1 (6.3)	2 (5.1)	3 (16.7)	5 (8.8)
FIL	1 (9.1)	2 (16.7)	0	3 (7.7)	0	3 (5.3)
OTHER	0	1 (8.3)	1 (6.3)	2 (5.1)	0	2 (3.5)
MCM	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)

Time since confirmed diagnosis (years) = (Date of diagnosis – index date +1)/365.25. Date of diagnosis is the date as entered in the eCRF. A patient may have multiple PROS subtypes.

Source: EPIK-P1-CSR-Table 14.1-3.2

The Applicant's Position:

Patients had heterogeneous manifestations of PROS. The subtype of PROS reported in the majority of the patients was CLOVES. The other subtypes of PROS reported in ≥ 5% patients were MCAP, KTS, and FIL. CLOVES and MCAP subtypes were concomitantly reported in four pediatric patients. The majority of patients had their disease diagnosed at birth. All, except one

patient with sporadic occurrence, had mosaic distribution of overgrowth (Table 14).

The FDA's Assessment:
In general, the FDA agrees with the description of the baseline demographic characteristics for the full study population. However, the FDA considers the summary of demographic and clinical characteristics for the efficacy population to be more relevant for the purposes of the efficacy evaluation, as presented in Table 13.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data and The Applicant's Position:
Treatment compliance: No treatment compliance measurement for alpelisib was performed due to the nature of the study. However, the information on how the drug was administered was collected from medical charts.
Concomitant medications: Details of concomitant medication and non drug therapies are described under the secondary objective of 'Changes in type of medication and non-drug therapies over time' in the section below.
Rescue medication: In EPIK-P1, treatment with alpelisib reduced the burden of invasive procedures, as indicated by a decrease in the incidence of PROS-related surgeries from five years prior to alpelisib initiation to the end of the study. No patient required rescue surgery by Week 24 due to disease progression. After the initiation of alpelisib treatment and until end of the study, two pediatric patients had surgeries due to disease progression which was not radiologically confirmed (Details are provided in the section below under the heading 'PROS related surgery').

The FDA's Assessment:
In general, the FDA agrees with the Applicant's description of documentation of treatment compliance and concomitant medications and non-drug therapies. In reference to use of rescue surgical procedures, the FDA cautions that although it is notable that no patients required rescue surgery by Week 24 due to disease progression, given the single-arm design of EPIK-P1, the heterogenous nature of PROS and the varying growth rates of related lesions, it is unclear whether disease progression necessitating rescue surgery would typically be observed in this time period. In the absence of randomization, one cannot necessarily conclude that absence of rescue surgery by Week 24 is due to treatment with alpelisib.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:
Definitions of study populations are given in Figure 4. The primary efficacy presented below are based on the complete case analysis (N=32).

Figure 4: Study population

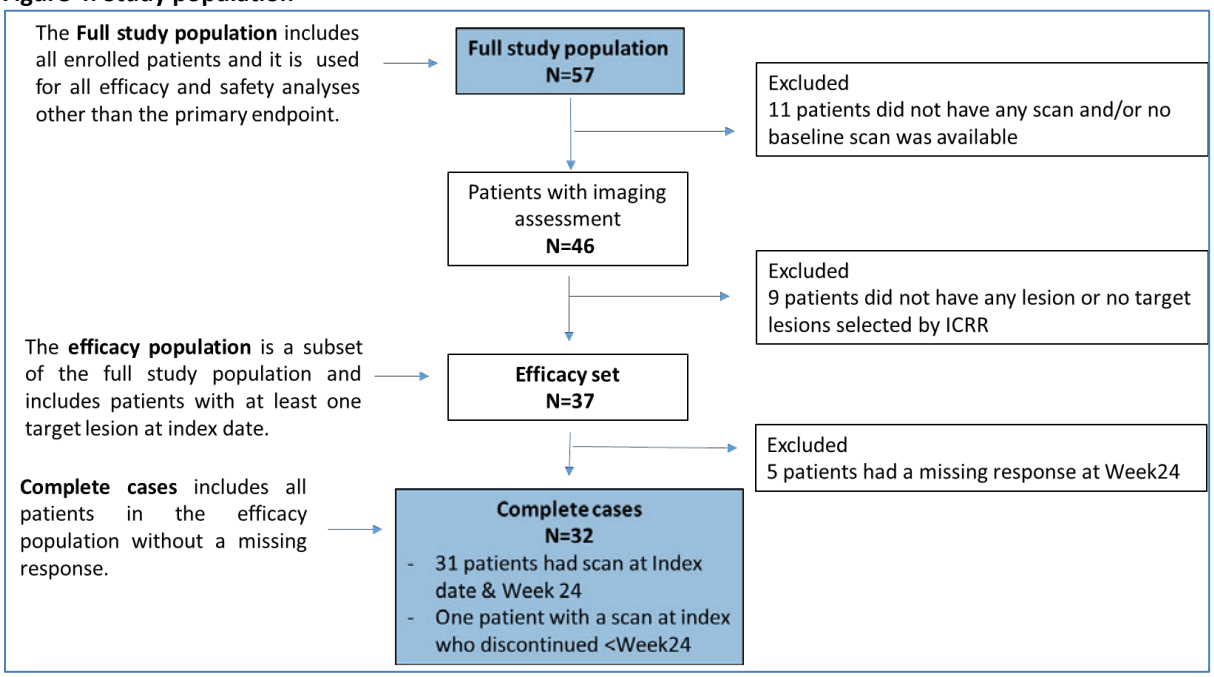


Table 16: Proportion of responders at Week 24 with complete cases (Efficacy population, complete case)

	All patients N=32	
Category	**n (%)**	**(95% CI)**
Responders[1]	12 (37.5)	(21.1, 56.3)
Non responders	20 (62.5)	(43.7, 78.9)

2-sided 95% Confidence Intervals (CI) are based on the exact (Clopper-Pearson) method.

[1]Response is defined by achieving at least 20% reduction from the index date in the sum of measurable target lesion volume provided that none of the individual target lesions have at least 20% increase and in absence of progression of non-target lesions and without new lesions. Also, patients did not permanently discontinue alpelisib prior to 24 weeks of treatment and did not require surgery as rescue therapy between index date and 24 weeks of treatment with alpelisib due to disease deterioration.

Complete cases are defined as the patients in the efficacy population without a missing response.

Patients were considered as having a missing response if lesion volume(s) assessment at 24 weeks or 6 months (+/- 4 weeks) is not available and did not permanently discontinue alpelisib prior to 24 weeks of treatment and did not require surgery as rescue therapy between the index date and 24 weeks of treatment with alpelisib due to disease deterioration.

Source: EPIK-P1-CSR-Table 14.2-2.1

The Applicant's Position:

Compelling evidence of efficacy is provided with alpelisib treatment in patients with PROS, as demonstrated by a clinically meaningful response rate in a rare population with a high unmet medical need (Table 15).

Data:

Table 17: Proportions of responders at Week 24 with complete cases - subgroup analyses (Efficacy population, complete case)

Subgroup Category	N	Responder (%)	95% CI
All patients	32	12 (37.5)	(21.1,56.3)
Pros subtype			
CLOVES	26	12 (46.2)	(26.6,66.6)
FIL [Facial Infiltrating Lipomatosis]	3	0	(0.0,70.8)
KTS [Klippel-Trenaunay Syndrome]	1	0	(0.0,97.5)
MCAP [Megalencephaly-Capillary Malformation]	3	0	(0.0,70.8)
Other	1	0	(0.0,97.5)
Mutation type			
Frequent	22	11 (50.0)	(28.2,71.8)
Less-frequent	10	1 (10.0)	(0.3,44.5)
Lesion type			
Abdominal Region	10	7 (70.0)	(34.8,93.3)
Brain	1	0	(0.0,97.5)
Chest	2	1 (50.0)	(1.3,98.7)
Head	5	0	(0.0,52.2)
Limb	2	0	(0.0,84.2)
Lower Leg	10	4 (40.0)	(12.2,73.8)
Neck	2	0	(0.0,84.2)
Other	1	1 (100)	(2.5,100.0)
Pelvis	7	4 (57.1)	(18.4,90.1)
Skin	1	0	(0.0,97.5)
Spinal/Paraspinal	2	1 (50.0)	(1.3,98.7)
Upper Arm	2	1 (50.0)	(1.3,98.7)
Upper Leg	2	0	(0.0,84.2)
Age (years)			
2-5	7	2 (28.6)	(3.7,71.0)
6-11	7	1 (14.3)	(0.4,57.9)
12-17	9	4 (44.4)	(13.7,78.8)
<18	23	7 (30.4)	(13.2,52.9)
≥18	9	5 (55.6)	(21.2,86.3)
Sex			
Male	13	5 (38.5)	(13.9,68.4)
Female	19	7 (36.8)	(16.3,61.6)
Body Weight(kg) in pediatric patients			

Subgroup Category	N	Responder (%)	95% CI
<20	4	1 (25.0)	(0.6,80.6)
20-<40	4	0	(0.0,60.2)
40-<60	7	2 (28.6)	(3.7,71.0)
≥60	4	2 (50.0)	(6.8,93.2)
Missing	4	2 (50.0)	(6.8,93.2)
Diabetic status			
Diabetic	1	1 (100)	(2.5,100.0)
Pre-diabetic	3	1 (33.3)	(0.8,90.6)
Normal	24	8 (33.3)	(15.6,55.3)
Unknown	4	2 (50.0)	(6.8,93.2)
Prior treatment status			
Pre-treated	19	11 (57.9)	(33.5,79.7)
Treatment naive	13	1 (7.7)	(0.2,36.0)

2-sided 95% Confidence Intervals (CI) are based on the exact (Clopper-Pearson) method.

Response is defined by achieving at least 20% reduction from the index date in the sum of measurable target lesion volume provided that none of the individual target lesions have ≥ 20% increase and in absence of progression of non-target lesions and without new lesions. Also, patients did not permanently discontinue alpelisib prior to 24 weeks of treatment and did not require surgery as rescue therapy between index date and 24 weeks of treatment with alpelisib due to disease deterioration.

Complete cases are defined as the patients in the efficacy population without a missing response.

Patients are considered as having a missing response if lesion volume(s) assessment at 24 weeks or 6 months (± 4 weeks) is not available and did not permanently discontinue alpelisib prior to 24 weeks of treatment and did not require surgery as rescue therapy between the index date and 24 weeks of treatment with alpelisib due to disease deterioration.

PROS subtypes were grouped as recorded in the eCRF. Patients may have more than one subtype.

Lesion types refers to the anatomical location of the lesion selected by ICRR. Patients may have more than one lesion type.

Source: EPIK-P1-CSR-Table 14.2-2.3

The Applicant's Position:

Across patients included in the complete cases analysis, the results from the subgroup analyses (prior treatment status and age category, body weight in pediatric patients, index date diabetic status, age category, response state [responders vs non-responders]) showed overall consistency in response rate at Week 24 (Table 16).

Sensitivity analysis

Data:

Table 18: Sensitivity analyses

Analyses Criteria	Responders n (%)	Responders (95% CI)
Sensitivity analysis 1 (N=37) The missing volumetric assessments at Week 24 were **multiply imputed** for patients with missing response	14 (36.7%)	(20.6, 52.9)
Sensitivity analysis 2 (N=37)		
Best-case scenario: Patients with missing responses at 24 weeks or 6 months (± 4 weeks) were considered as **'responders'**	17 (45.9%)	(29.5, 63.1)
Sensitivity analysis 3 (N=37)		
Worst-case scenario: Patients with missing responses at 24 weeks or 6 months (± 4 weeks) were considered as **'non-responders'**	12 (32.4%)	(18, 49.8)
Sensitivity analysis 4 (N=15)		
Modified scan window: sensitivity analyses of the primary endpoint of response rate using the initially defined scan windows for the baseline scan (up to 12 weeks prior to the index date) and the 24-week response assessment (between 20 and 28 weeks).	3 (20.0%)	(4.3, 48.1)

Source: EPIK-P1-CSR-Table: 14.2-2.3

The Applicant's Position:

The results of sensitivity analyses also demonstrated similar response rates at Week 24 with the primary analyses, except for sensitivity analysis 4, possibly due to the small number of patients (Table 17).

As per correspondence with the FDA and consistent with the suggestion of the Agency, the sensitivity analysis 3 is based on the efficacy analysis set in which patients with missing response at 24 weeks or 6 months (+/- 4 weeks) are considered as "non-responders''.

The FDA's Assessment:

As described previously, the FDA considers the efficacy population to include all patients with at least one target lesion and with an imaging scan performed on the index date (or up to 24 weeks prior to the index date) for at least one target lesion, regardless of capture of response at Week 24. This results in an efficacy population of 37 patients.

In addition, the FDA considers the primary endpoint to be confirmed response rate. The FDA's primary efficacy analysis using confirmed response in the efficacy population described above (N=37) is presented in Table 19.

Table 19. Primary Efficacy Analysis of Overall Response Rate in Efficacy Population

	Pediatric N=26	Adult N=11	All Population N=37
Overall Response Rate[1], n (%)	7 (27)	3 (27)	10 (27)
95% CI	(12, 48)	(6, 61)	(14, 44)
Duration of response			
Median in months (range)	NR (2.8+, 29.7+)	NR (0.9+, 42.9+)	NR (0.9+, 42.9+)
Patients with at least 6-month response, n(%)	5 (71)	2 (67)	7 (70)
Patients with at least 12-month response, n(%)	5 (71)	1 (33)	6 (60)
Patients with at least 24-month response, n(%)	2 (29)	1 (33)	3 (30)

There were two patients (ID #s (b) (6) who did not have confirmed responses that were included as responders in the Applicant's analysis but were not considered responders in the FDA analysis. Both patients were diagnosed with CLOVES and harbored a "frequent" PIK3CA mutation. It is noteworthy that both patients were treated for prolonged periods (Patient (b) (6) for 578 days with treatment ongoing at data cut-off, and Patient (b) (6) for 371 days before discontinuation per patient decision). Patient (b) (6) had 38% shrinkage in the sum of target lesion volumes at Week 24 by BICR but lacked follow-up imaging of the same anatomical location of the target lesions located at index date, precluding confirmation of response. Patient (b) (6) demonstrated 22% shrinkage in the sum of target lesion volumes, and per review of the corresponding case narrative, appears to have had improvement in symptoms related to PROS (e.g., resolution of pain, decreased bleeding, correction of anemia) from alpelisib treatment.

Additional FDA analyses include selected subgroup analyses of confirmed response rate (Table 20). It is noteworthy that all patients had surgery previously, so this subgroup is not presented in this table. Overall, these subgroup analyses should be interpreted with caution given the small sample sizes and retrospective data capture, but provide some evidence of consistency of treatment effect.

Table 20: Subgroup analyses for Overall Response Rate in Efficacy Population

	N	Responder n (%)	95% CI
Age			
Age 2-5	8	2 (25)	(3.2, 65)
Age 6-11	8	1 (12.5)	(0.3, 53)
Age 12-17	10	4 (40)	(12, 74)
Adult (18+)	11	3 (27)	(6, 61)
Sex			
Female	21	6 (29)	(11, 52)
Male	16	4 (25)	(7, 52)
PROS Subtypes			
CLOVES	30	10 (33)	(17, 53)
MCAP, KTS, FIL and Others	7	0	--
Mutation Type			
Frequent	25	9 (36)	(18, 57)
E542K	9	5 (56)	(21, 86)
H1047R	6	2 (33)	(4.3, 78)
H1047L	2	1 (50)	(1.3, 99)
C420R	5	1 (20)	(0.5, 72)
E545K, N345K, T1025A	7	0	--
Less-frequent	12	1 (8)	(0.2, 38)
E545A, E545G, E545K	5	0	--
Other	7	1	(0.4, 58)
Prior use of sirolimus			
No	18	3 (17)	(3.6, 41)
Yes	19	7 (37)	(16, 62)
Prior use of taselisib			
No	32	9 (28)	(14, 47)
Yes	5	1 (20)	(0.5, 72)

Note: Subgroup analyses were not performed based on race, ethnicity, or performance status due to the extent of missing information for these demographic parameters.

Data Quality and Integrity

Data and The Applicant's Position:
There were no known Health Authority inspections conducted at investigator sites participating in this study.

The FDA's Assessment:
Refer to Section 4.1 regarding inspections conducted by the Office of Scientific Investigations.

Trial monitoring, data collection methods and data quality assurance procedures are summarized above in the section "Compliance with Good Clinical Practices". The EPIK-P1 Clinical Study Report (submitted in Module 5.3.5.4) also details the following:

- Quality control measures implemented throughout development and implementation of the electronic case report form (eCRF), including data validation checks
- The EDC platform (compliant with 21 CFR Part 11), a data capture software that was used to develop the eCRF and features electronic data capture, data change tracking, electronic signatures, and audit trail capabilities. Per the Applicant, the software allows for the creation of data checks to support data quality; post-hoc manual review of data for outliers and inconsistencies; and incorporates a query log and audit log to document changes in data during the quality control process. The EDC also includes implementation of a database lock (e.g., following review, and verification, of the data, the CRF of each patient on the EDC system will be locked after investigator signature has been obtained on the data entered). Following a database lock, the EDC database was archived and stored on secure storage.
- The data management process that was pre-specified in a data management plan (DMP)
- Physician maintenance of source documents (medical records containing case and visit notes and the results of tests or assessments) for each patient in the study as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8), and the traceable nature of these source documents when information is entered into the eCRF
- Formal site monitoring and compliance that was assured by the Applicant's trial monitoring team

Additionally, the EPIK-P1 clinical protocol (submitted in Module 16.1.1) describes the process by which patient-level data (including imaging scans [i.e., MRI and CT scans], clinical photographs and/or videos, as available) was abstracted from medical charts by trained personnel, sent to the contracted vendor, entered into the eCRF and used to generate physician narratives. A Data Quality Plan describing the processes and practices associated with data collection and management was also submitted.

Based on these study features, the FDA considers the data provided in the submission to be reliable and complete, to the extent possible. The Applicant's submission contained all of the

required components of the electronic Common Technical Document (eCTD) and was of adequate quality and integrity to allow for review of the study data supporting the proposed indication. The results from the primary safety and efficacy datasets were reproducible. The FDA was able to confirm the Applicant's analyses of the key primary and secondary endpoints discussed in this review and inspections conducted by OSI did not reveal significant concerns regarding the data.

Efficacy Results – Secondary and other relevant endpoints

I. Change in sum of measurable target lesion volume

Data:

Table 21: Change and percent change in the sum of target lesion volume over time by age category (Full study population)

		Pediatric patients (<18 years) N=39			Adult patients (≥ 18 years) N=18			All patients N=57		
Time point	**Statistics**	**Visit Value**	**Change**	**% Change**	**Visit Value**	**Change**	**% Change**	**Visit Value**	**Change**	**% Change**
Index date	n	26			11			37		
	Mean	1088.65			2482.85			1503.14		
	SD	1383.202			2306.583			1795.514		
	Min	2.6			16.6			2.6		
	Median	643.81			2106.08			735.18		
	Max	4718.6			6941.7			6941.7		
12 weeks	n	14	14	14	4	4	4	18	18	18
	Mean	722.64	-129.13	-18.59	498.29	-139.10	-19.77	672.78	-131.35	-18.85
	SD	1038.423	140.046	16.837	573.737	157.627	5.128	944.404	139.287	14.888
	Min	14.7	-376.2	-51.2	97.8	-351.9	-26.2	14.7	-376.2	-51.2
	Median	413.85	-77.94	-14.09	287.63	-93.12	-19.31	412.01	-77.94	-17.17
	Max	4095.5	5.0	0.4	1320.1	-18.3	-14.2	4095.5	5.0	0.4
24 weeks	n	22	22	22	9	9	9	31	31	31
	Mean	694.61	-60.34	-11.20	2402.67	-442.46	-19.69	1190.50	-171.28	-13.66
	SD	921.295	134.045	19.987	2279.255	508.897	15.375	1612.643	335.746	18.921
	Min	14.7	-419.7	-57.1	114.6	-1498.1	-45.8	14.7	-1498.1	-57.1
	Median	312.09	-25.16	-3.58	2350.89	-326.95	-20.93	503.14	-30.58	-9.01
	Max	3764.6	114.5	15.0	7037.3	95.6	1.4	7037.3	114.5	15.0

		Pediatric patients (<18 years) N=39			Adult patients (≥ 18 years) N=18			All patients N=57		
Time point	**Statistics**	**Visit Value**	**Change**	**% Change**	**Visit Value**	**Change**	**% Change**	**Visit Value**	**Change**	**% Change**
52 weeks	n	16	16	16	4	4	4	20	20	20
	Mean	658.78	-110.31	-13.91	3775.38	-232.01	-6.52	1282.10	-134.65	-12.43
	SD	735.975	155.860	19.206	2235.125	99.864	2.614	1688.888	152.471	17.363
	Min	15.7	-452.7	-53.0	1568.7	-339.4	-9.3	15.7	-452.7	-53.0
	Median	396.02	-56.76	-10.46	3402.79	-242.68	-6.87	713.46	-107.26	-8.41
	Max	2491.3	121.7	17.2	6727.3	-103.3	-3.1	6727.3	121.7	17.2
End of study	n	4	4	4	3	3	3	7	7	7
	Mean	429.59	-305.56	-36.47	3039.18	-549.25	-17.38	1547.99	-410.00	-28.29
	SD	351.086	514.679	46.137	1598.210	444.724	11.679	1690.787	464.047	34.841
	Min	110.6	-1046.8	-85.9	1246.0	-1042.6	-25.5	110.6	-1046.8	-85.9
	Median	377.99	-160.13	-40.25	3558.01	-425.95	-22.66	851.75	-179.18	-22.66
	Max	851.8	144.8	20.5	4313.5	-179.2	-4.0	4313.5	144.8	20.5

Percent Change at week X = ((Sum(voume1_Xweeks,volume2_Xweeks,volume3_Xweeks) Sum(volume1_index,volume2_index,volume3_index)))/(Sum(volume1_index,volume2_index,volume3_index)) x 100.
The index date will be defined as the date of alpelisib initiation (or up to 12 weeks prior).
At each time point, only patients with a value at both index date and that time point are included in the calculation of change.
Visit value is defined as the sum of the lesion volume at that timepoint
Source: EPIK-P1-CSR-Table 14.2-3.1

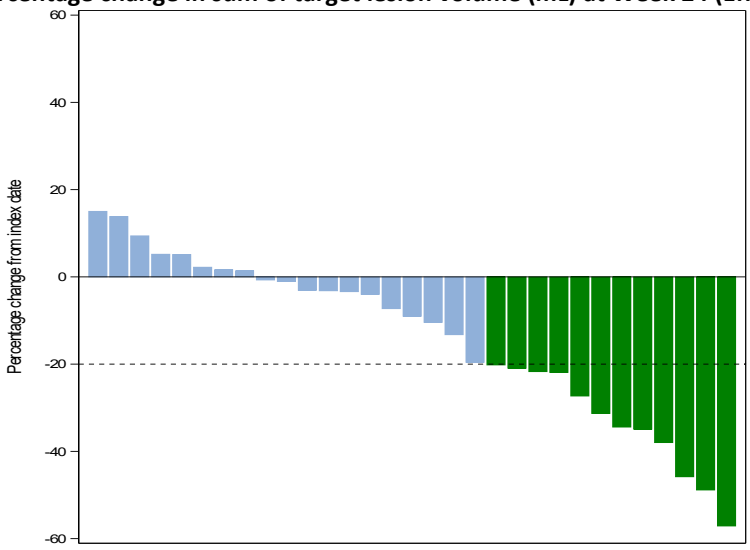
The Applicant's Position:

The results of the secondary efficacy analyses are supportive of the primary analysis results.

Across patients included in the primary analysis with available radiological assessments at the index date and at Week 24, the majority of patients (74.2%) had any reduction in the sum of target lesion volume assessed by the ICRR (Table 21).

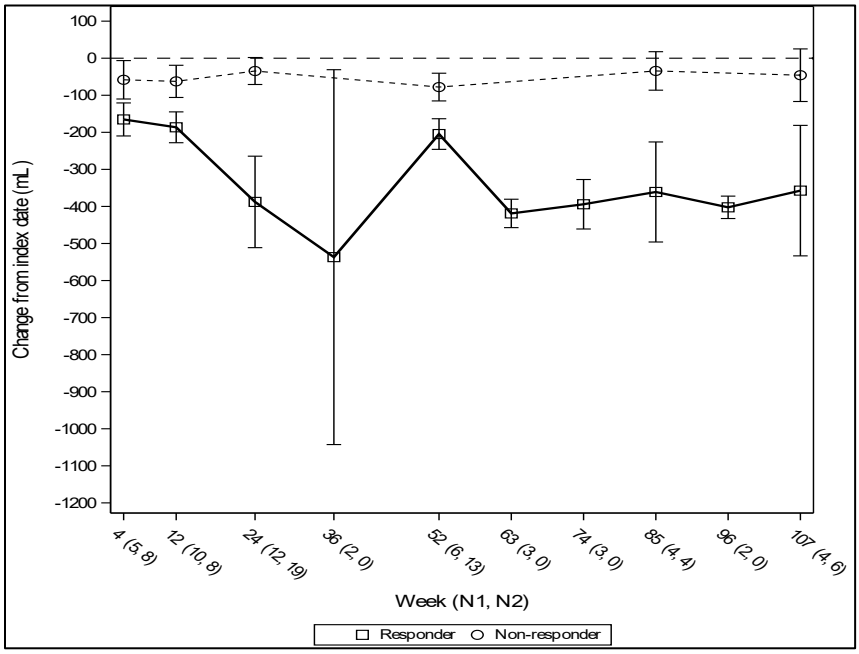
Subgroup analysis: The results from subgroup analyses (prior treatment status and age category, the pre-index date diabetic status and age category (Table 16), response state [responders vs non-responders]) showed overall consistent reduction in the sum of target lesion volume (Figure 5 and Figure 6).

Figure 5: Individual percentage change in sum of target lesion volume (mL) at Week 24 (Efficacy population)



Patients who are responders for the primary endpoint are highlighted in green. Non-responders are highlighted in blue. Source: [PROS CO-Appendix 2-Figure 3.1-1.5].

Figure 6: Mean (+/-SE) change in the sum of target lesion volume (mL) over time by primary endpoint response status (Efficacy population)



(N1, N2) presents the number of responders and non-responders respectively with an assessment at that visit. Source: [PROS CO-Appendix 2-Figure 3.1-1.2]

II. Change in sum of all measurable (target and non-target) lesion and all measurable non-target lesion volume

As no measurable non-target lesions were identified, the results for changes in the sum of all measurable (target and non-target) lesion volume were identical to the results presented above.

III. Change in sum of all measurable non-target lesion volume

No measurable non-target lesions were identified by ICRR at the index date.

IV. Changes in type of medication and non-drug therapies over time

a) Concomitant PROS related medications

All patients (N=57):
Concomitant medication administered was representative of that routinely prescribed for patients with PROS. Treatment with alpelisib was associated with a gradual reduction in the use of concomitant medications to manage PROS (index date: 34/57 patients, 59.6%; Week 24: 30/56 patients, 53.6 %; end of study 25/57 patients, 43.9%).
In the Pre index period (N=57): Forty-two patients (73.7%) were administered PROS-related medication during the 24 weeks of the pre-index period. Concomitant PROS-related medications used by ≥ 20% of the patients by ATC class were attributed to antineoplastic and immunomodulating agents (24 patients, 42.1%), of which the most reported medications (>5%) were sirolimus (18 patients, 31.6%) and taselisib (6 patients, 10.5%); nervous system (19 patients, 33.3%) with the most reported medication (>5%) being paracetamol (9 patients, 15.8%), gabapentin (3 patients, 5.3%), and tramadol (3 patients, 5.3%); and blood and blood forming organs (15 patients, 26.3%) with the most reported medication (>5%) being fondaparinux sodium (5 patients, 8.8%), enoxaparin sodium (4 patients, 7%), apixaban (3 patients, 5.3%) [PROS EPIK-P1-CSR-Table 14.1-4.4].
In the study period (N=57): Overall, during the study period, 45 (78.9%) patients had at least one concomitant medication during the complete course of the study, of which 38 patients received PROS-related medication. Concomitant PROS-related medications used by ≥ 20% of the patients by ATC class at Week 24 were attributed to nervous system (18 patients, 32.1%) with the most reported medication (>5%) being paracetamol (10.7%), tramadol (7.1%), and gabapentin (5.4%); alimentary tract and metabolism (16 patients, 28.6%) with the most reported medication (>5%) being colecalciferol (8.9%), and macrogol (7.1%); and blood and blood forming organs (15 patients, 26.8%) with the most reported medication (>5%) being fondaparinux sodium (10.7%), ferrous sulfate (5.4%), and apixaban (5.4%) [PROS EPIK-P1-CSR-Table 10-15].

b) **Pain medication**: In the Full study population (N=57), the percentage of patients receiving pain medication (including opioids) remained stable from the index date to the end of the study (index date: 18/57 patients, 31.6%; vs. Week 24: 17/56 patients, 30.4%; vs. Week 52: 13/52 patients, 25%; vs. Week 74: 9/38 patients, 23.7%) [PROS EPIK-P1-CSR-Table 14.3-2.11].

c) **PROS related non drug treatments and other medical interventions**: As a conservative approach, the non-drug therapies with missing start and end dates or with only missing start date, were assumed to be reported during the study period. This approach impacts the association of the event to the correct period of time and impacts the interpretation of the below results.

All patients (N=57)

The number of patients receiving PROS related non-drug treatments and other medical interventions remained consistent over time (index date: 32/57 patients (56.1%) vs. Week 24: 32/56 patients, 57.1% vs. Week 52: 29/52 patients, 55.8%; vs. Week 74: 20/38 patients, 52.6% [PROS EPIK-P1-CSR-Table 14.3-2.13].

In the pre-index period (all patients (N=57), types of supportive non-drug treatments received by ≥ 5% of the patients were compression garments (12 patients, 21.1%); supportive mobility devices excluding wheel-chair (five patients, 8.8%); and wheel-chair (five patients, 8.8%) [PROS EPIK-P1-CSR-Table 14.1-4.6].

In the study period (all patients (N=57), 48 patients (84.2%) had received at least one PROS related non-drug treatments and other medical interventions. Types of supportive non-drug treatments received by ≥ 5% of the patients were compression garments (23 patients, 40.4%); supportive mobility devices excluding wheelchair (10 patients, 17.5%); wheel-chair (nine patients, 15.8%); blood transfusion (three patients, 5.3%); and sclerotherapy (three patients, 5.3%). Of note, due to the conservative approach taken to analyze data (missing or partial start or end dates), a total of nine patients are reported to require wheel-chair assistance during study period. Of these, four patients had improvement and stopped using wheel-chair under alpelisib treatment [PROS EPIK-P1-CSR-Table 14.3-2.12 and Table 14.3-2.13].

d) **PROS related surgery**

All patients (N=57)

Diagnosis to the start of the pre-index date period (24 weeks prior to the start of alpelisib):

Fifty patients (87.7%) underwent at least one surgery. The median number of surgeries per patient was four (range: 1 to 15) and 37 patients (64.9%) had more than two surgical procedures. A total of 255 surgical procedures were performed of which debulking (141 procedures) was the most frequent, followed by functional surgeries (27 procedures), amputation (22 procedures) and vascular surgeries (21 procedures). Disease progression was the main reason for surgery (92.2% of the surgeries) [PROS EPIK-P1-CSR-Table 14.1-4.3].

Pre-Index period (all patients, N=57): Five patients (8.8%) had at least one surgery during the 24 weeks of the pre-index period. Three patients had debulking, one patient had embolization at the limb, and one patient had four surgeries: two debulking surgeries and two cosmetic surgeries. All surgical procedures were indicated due to PROS disease progression. These five patients who had multiple surgeries since diagnosis, did not have any surgery after the initiation of alpelisib [PROS EPIK-P1-CSR-Listing 16.2.4-1.4].

Study Period (all patients, N=57): There were no rescue surgeries (i.e. due to disease progression) within the first 24 weeks or 6 months (± 4 weeks)of treatment. Seven patients (12.3%; five pediatric and two adults) underwent a total of 11 surgical procedures following the initiation of alpelisib treatment. Three of the seven patients had ≥ two surgeries. Surgery due to disease progression was reported in two patients and due to disease improvement in three patients, respectively. "Disease improvement" indicates that a patient who was previously not eligible for a surgical procedure became eligible following alpelisib treatment [PROS EPIK-P1-CSR-Table 10-16 and Listing 16.2.4-1.4].

Pediatric patients (N=39)

Diagnosis to the start of the pre-index date period (24 weeks prior to the start of alpelisib): Thirty-three pediatric patients (84.6%) underwent at least one surgery between diagnosis and the start of the pre-index period. The median number of surgeries per patient was four (range: 1 to 15) and 24 patients (61.5%) had more than two surgical procedures. A total of 172 surgical procedures were performed of which debulking (91 procedures) was the most frequent, followed by functional surgeries (23 procedures), other type of surgeries (22 procedures), amputation (13 procedures), vascular and epiphysiodesis surgeries (seven procedures each), cosmetic (six procedures), and scoliosis (three procedures). Disease progression was the main reason for surgery (94.2% of the surgeries) [PROS EPIK-P1-CSR-Table 14.1-4.3].

Pre-index period: Four pediatric patients (10.3%) had at least one surgery. Two patients had debulking, one patient had embolization at the limb, and one patient had four surgeries: two debulking surgeries and two cosmetic surgeries. All four surgical procedures were indicated due to PROS disease progression [PROS EPIK-P1-CSR-Table 14.1-4.2].

Study period: Five pediatric patients (12.8%) underwent a total of 8 surgical procedures following the initiation of alpelisib treatment out of which 2 patients underwent surgeries due to clinical disease progression (not radiologically confirmed), however these patients continued treatment with alpelisib as they derived clinical benefit.

Adult patients (N=18)

Diagnosis to the start of the pre-index date period (24 weeks prior to the start of alpelisib)

Seventeen adult patients (94.4%) underwent at least one surgery between diagnosis and the start of the pre-index period. The median number of surgeries per patient was four (range: 1 to 15) and 13 patients (72.2%) had more than two surgical procedures. A total of 110 surgical procedures were performed of which debulking (50 procedures) was the most frequent, followed

by other type of surgeries (22 procedures), vascular surgeries (14 procedures), amputation (nine procedures), scoliosis (five procedures), functional surgeries (four procedures), epihysiodesis (three procedures), cosmetic (two procedures), and unknown (one procedure). Disease progression was the main reason for surgery (89.1% of the surgeries) [PROS EPIK-P1-CSR-Table 14.1-4.3].

Pre-index period

One adult patient (5.6%) had debulking surgery during the pre-index period due to disease progression [PROS EPIK-P1-CSR-Table 14.1-4.2].

Study period

Two adult patients (11.1%) underwent a total of three surgical procedures (one patient had surgery in the abdominal region explained by the shrinkage of the vascular malformation and the other patient had one functional surgery at thorax due to disease improvement and one cosmetic surgery due to delayed wound healing post-surgery) following the initiation of alpelisib treatment of which. None of the patients had a surgery performed within the first six months after start of alpelisib. No adult patient required surgery due to disease progression [PROS EPIK-P1-CSR-Table 10-16].

V. Changes in PROS symptoms and complications

Data:

Table 22: Most frequent PROS related signs and symptoms during the first 24 weeks (Full study population)

PROS-related signs or symptoms	Pediatric patients (<18 years) N=39		Adult patients (>=18 years) N=18		All patients N=57	
	Index	Improved[1] by Week 24	Index	Improved* by Week 24	Index	Improved* by Week 24
Fatigue	28 (71.8)	22 (78.6)	14 (77.8)	10 (71.4)	42 (73.7)	32 (76.2)
Vascular malformation	25 (64.1)	20 (80.0)	13 (72.2)	10 (76.9)	38 (66.7)	30 (78.9)
Disseminated intravascular coagulation	19 (48.7)	11 (57.9)	10 (55.6)	5 (50.0)	29 (50.9)	16 (55.2)
Limb asymmetry	17 (43.6)	11 (64.7)	12 (66.7)	9 (75.0)	29 (50.9)	20 (69.0)
Pain	12 (30.8)	11 (91.7)	10 (55.6)	9 (90.0)	22 (38.6)	20 (90.9)

[1] Improvement is defined based on CTC grade reduction or resolution of the event. % are calculated on the number of patients reporting the event at index date.

Source: EPIK-P1-CSR-Table 14.3-2.5

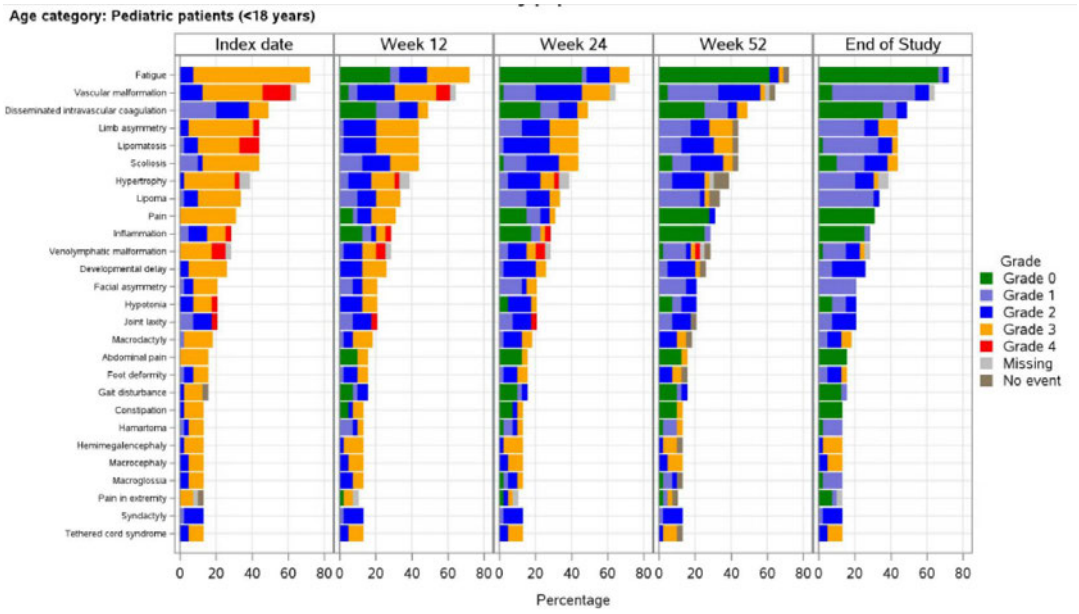
The Applicant's position:

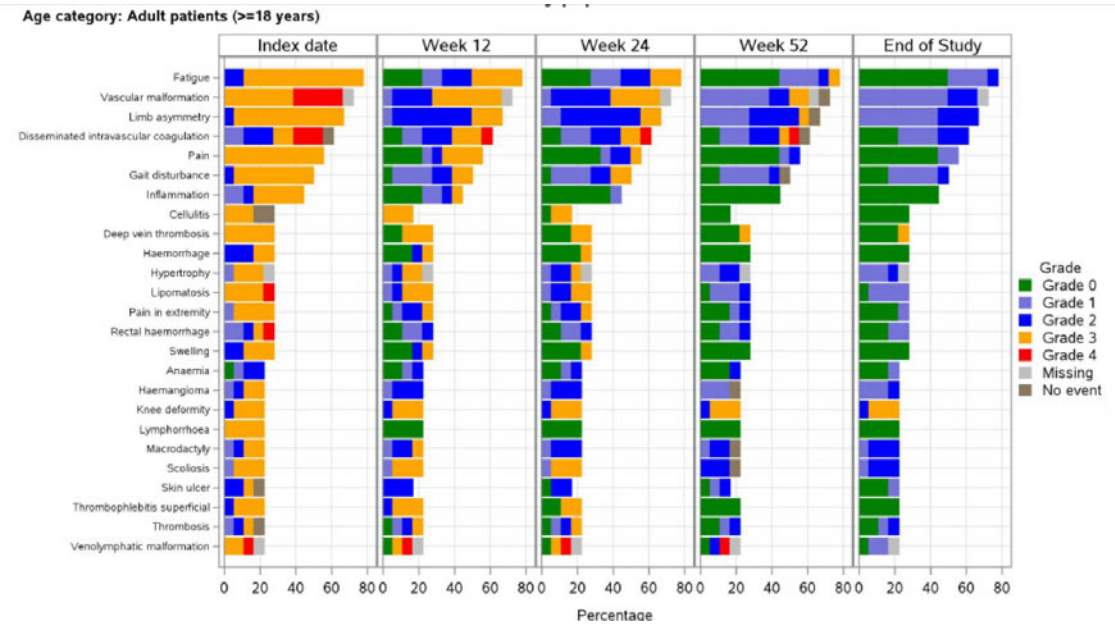
Improvement in PROS symptoms and complications was defined based on at least one grade reduction or resolution of the sign and symptoms, considering the Full study population. Evidence of clinically meaningful improvement in the signs and symptoms associated with PROS was reported across the overall population (N=57). These results demonstrate a positive treatment effect in patients with PROS. The majority of patients experienced improvement in their health status, functioning, and disease-related symptoms overtime after initiating alpelisib treatment (Table 21).

The evolution of the PROS-related signs and symptoms severity (including resolution – grade 0) is displayed at key time-points (i.e. at index date, Weeks 12, 24, 52, and at the end of the study) in Figure 7.

Marked reductions in the number of grade 3/4 signs and symptoms over time were observed. This improvement in the five most frequent complications was consistent across age groups and sustained over time as demonstrated in the Figure 7.

Figure 7: Shift in CTC grade from index date to key post-index visits of the most frequent PROS-related signs and symptoms by age category (Full study population)





The top 20 PROS-related signs and symptoms are based on the frequency reported in pediatric and adult patients.

X- Axis reports percentage of the pediatric and adults respectively. Grade refers to CTC grading.

An event is defined as resolved (Grade 0) if there is an end date in that time interval with no subsequent event in the same interval (e.g., for Week 24, the time interval is from Week 20 to Week 31).

Missing refers to a missing CTCAE grade for an event. End of study refers to the full study period.

No event at the index date means that there was no event present at the index date, but an event subsequently occurred on the study (adverse event). No event at other time points means that a patient did not reach that time point on the study.

Source: [PROS EPIK-P1-CSR-Figure 14.3-1.2]

Pain (composite endpoint)

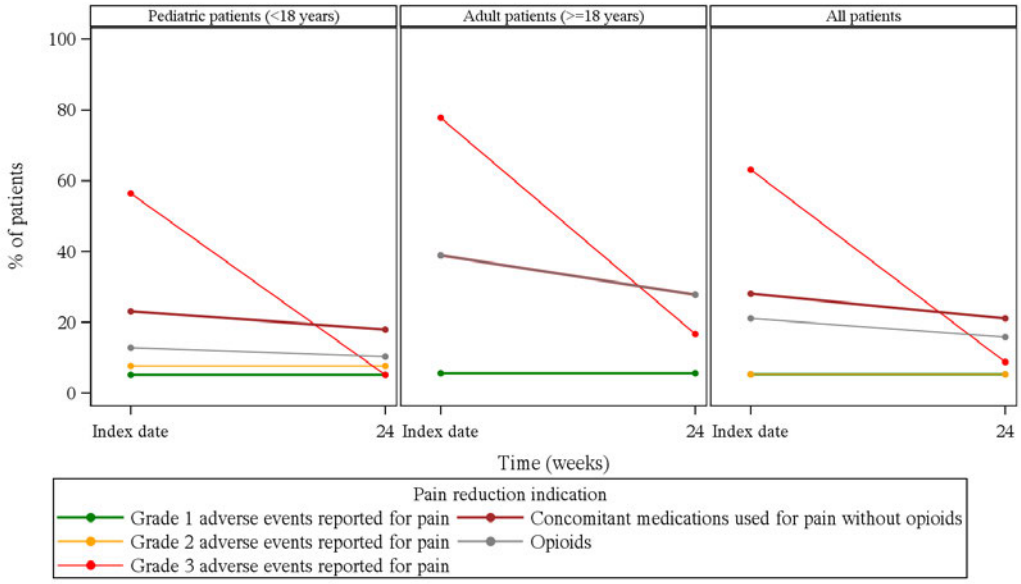
A questionnaire recording pain severity (i.e. Wong Baker, FLACC and Numerical scale rating) was collected for 11/57 patients (6 pediatric and 5 adult patients). Of these, six patients had completed the questionnaires at Week 24, all of them remained stable with no pain.

Pain or its management was not consistently reported across patients and some data points were missing (start or end date) making the evaluation of pain overtime difficult. To further assess pain reduction at the Week 24 time point a composite end point was created. Pain reduction was considered, if improvement was reported for at least one of the following items provided that none of the other items was associated with a deterioration during the same period:

- pain score from the questionnaire,
- number of concomitant medications excluding opioids,
- number of opioids,
- number and severity of pain related medical conditions/treatment emergent AEs.

A marked reduction in grade 3 pain was reported in all patients over time (Figure 8).

Figure 8 Reduction in pain at Week 24 (Full study population)



Composite endpoint elaborated to assess incidence of pain takes into account: the number of concomitant medications used for pain; opioids used for pain, the severity and number of pain related signs and symptoms, the pain score from the pain severity questionnaire (where available). The figure shows the evolution of each component of the composite endpoint. Adverse events refers to AE and medical conditions pre-existing at the index date.

Y axis reports the percentage of patients.

Source: [PROS EPIK-P1-CSR-Figure 14.3-1.5]

Change in functional status

Data:

Table 23: Change in performance status score overtime by age category (Full study population)

	Pediatric patients (< 18 years) N=39	Adult patients (>= 18 years) N=18	All patients N=57
Number of patients with PS at index date - n(%)	33 (84.6)	14 (77.8)	47 (82.5)
Index date - ECOG			
n	3	0	3
Mean (SD)	1.7 (1.53)	NA (NA)	1.7 (1.53)
Median	2.0	NA	2.0
Min-Max	0-3	NA-NA	0-3
Index date – Lansky			
n	24	0	24
Mean (SD)	68.8 (18.01)	NA (NA)	68.8 (18.01)
Median	70.0	NA	70.0

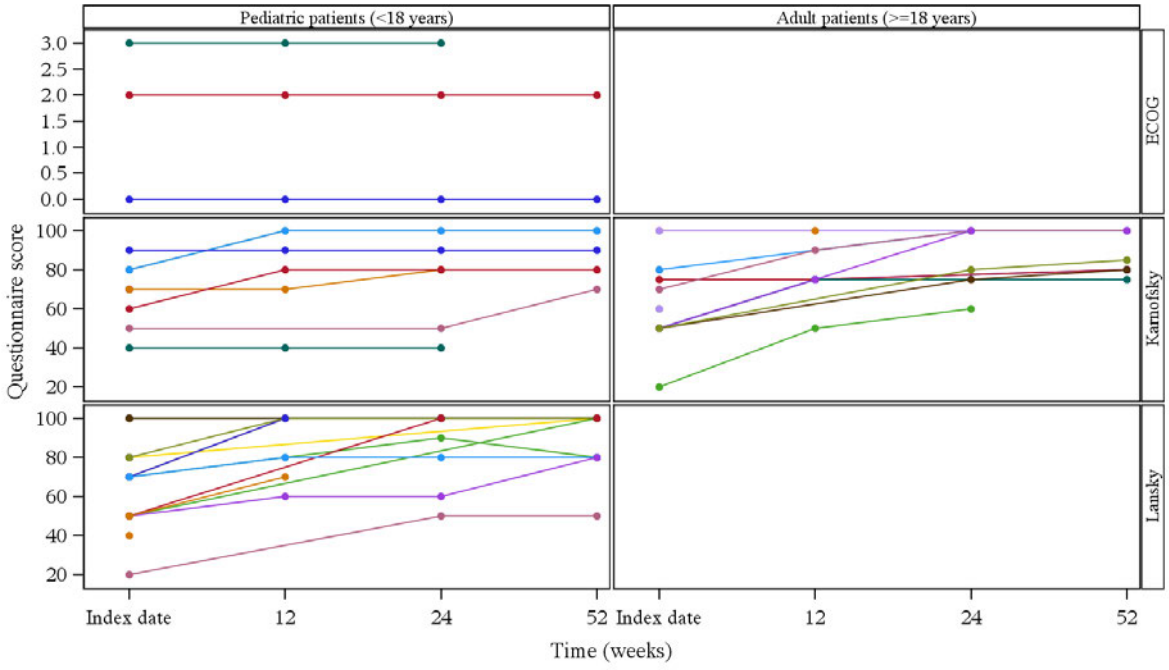
Min-Max	20-100	NA-NA	20-100
Index date – Karnofsky			
n	9	14	23
Mean (SD)	67.8 (15.63)	63.9 (21.85)	65.4 (19.36)
Median	70.0	60.0	70.0
Min-Max	40-90	20-100	20-100
Change in score (% of patients) Week 24			
Stable	9 (27.3)	1 (7.1)	10 (21.3)
Improved	8 (24.2)	6 (42.9)	14 (29.8)

PS: Performance status. Source: EPIK-P1-CSR-Table 14.3-4.1

The Applicant's position:

Treatment with alpelisib was associated with improvement in functional status at Week 24 including improved performance status (ECOG, Lansky, Karnofsky score) (Table 22). Improvement in the score was sustained at Week 52 and end of study (Figure 9).

Figure 9: Change in performance assessments by age and overtime (Full study population)



The graph is showing individual patient data.
The Eastern Cooperative Oncology Group (ECOG) score runs from 0 to 5, with 0 denoting perfect health and 5 death.
The Karnofsky Performance Score (KPS) and Lansky score run from 0 to 100, where 0 is death and 100 is perfect health.

Source: EPIK-P1-CSR-Figure 14.3-1.4

Mobility
Given the retrospective nature of the study, mobility assessment using objective measurement or questionnaire was not performed for the majority of the patients (54/57; 94.7%), therefore no meaningful conclusions could be drawn [PROS EPIK-P1-CSR-Table 14.3-3.3].

School attendance and work status

School attendance:
All patients (N=57): School attendance was reported for 33 patients (57.9%) at the index date. Of these, 81.8% reported full-time (75% to 100%), 15.2% reported part-time (>0 to <75%) and 6.1% reported no attendance as school status at the index date. School attendance remained unchanged during the study period for the majority of patients. 32 patients (97.0%) at Week 24 and 29 patients (87.9%) at the end of the study had no change in their school attendance. Improvement in school attendance was reported for one patient (3.0%) at Week 24 and four patients (12.1%) at the end of the study [PROS EPIK-P1-CSR-Table 14.3-5.2].
Pediatric patients (N=39): School attendance was reported for 29/39 pediatric patients (74.4%) at the index date. Of these, 86.2% reported full-time (75% to 100%) and 13.8% reported part-time (>0 to <75%) as school status at the index date. School attendance remained unchanged during the study period for the majority of patients. 28 patients (96.6%) at Week 24 and 27 patients (93.1%) at the end of the study had no change in their school attendance. Improvement in school attendance was reported for one patient (3.4%) at Week 24 and two patients (6.9%) at the end of the study [PROS EPIK-P1-CSR-Table 14.3-5.2].
Adult patients (N=18): School attendance was reported for 4/18 adult patients (22.2%) at the index date. 50% reported full-time (75% to 100%) and 25% reported part-time (>0 to <75%) as school status at the index date. School attendance remained unchanged during the study period for the all the patients at Week 24 and two patients (50%) at the end of the study. Improvement in school attendance was reported for two patients (50%) at the end of the study.

Work status
Work status was reported for 8/18 adult patients (44.4%) at the index date. Of the total eight patients, part-time (defined as at least 1 and <35 hours/week) work status was reported for six patients (75%) at the index date.
Improvement in work status was reported for five patients (62.5%) at the end of the study. Work status was stable for six patients (75%) at Week 24 and two patients (25%) at the end of the study [PROS EPIK-P1-CSR-Table 14.3-5.2].

Change in Healthcare resource use (HRU)
All patients (N=57): During the 24 weeks of the pre-index period, seven patients (12.3%) were hospitalized due to PROS, while during the first 24 weeks after the initiation of treatment, six patients (10.5%) were hospitalized due to PROS, of whom one patient was permanently hospitalized in a rehabilitation center already prior to the pre-index period, two patients had surgeries, one patient had laryngotracheal endoscopy, one patient had cellulitis, and one

patient had thrombosis. Cellulitis was a serious, grade 3 adverse event which resolved, while thrombosis was reported as venous thrombosis of left sole grade 1 but classified as serious by the treating physician [PROS EPIK-P1-CSR-Table 14.1-4.8].

Sixteen patients (28.1%) were hospitalized for any reason while on treatment (median duration of treatment - 19 months), of them 12 patients were hospitalized due to PROS [PROS EPIK-P1-CSR-Table 14.3-6.1].

Pediatric patients (N=39): During the 24 weeks of the pre-index period, five pediatric patients (12.8%) were hospitalized due to PROS, while during the first 24 weeks after the initiation of treatment, three patients (7.7%) were hospitalized due to PROS, of whom one patient was permanently hospitalized in a rehabilitation center already prior to the pre-index period, two patients had surgeries, laryngotracheal endoscopy in one patient and surgery in another patient [PROS EPIK-P1-CSR-Table 14.1-4.8].

Ten pediatric patients (25.6%) were hospitalized for any reason while on treatment (median duration of treatment - 17 months), of them eight patients were hospitalized due to PROS. Reason for hospitalization included: two patients had surgery due to disease improvement, one patient had debulking surgery, one patient had a functional surgery for other reasons (not related to disease progression), two patients due to cellulitis, and one patient had laryngotracheal endoscopy. One patient was permanently hospitalized in a rehabilitation center already prior to the pre-index period [PROS EPIK-P1-CSR-Table 14.3-6.1].

Adult population (N=18): During the 24 weeks of the pre-index period two adult patients (11.1%) were hospitalized, all due to PROS, while during the first 24 weeks after the initiation of treatment, three patients were hospitalized due to PROS, three patients had surgeries, surgical removal of spine prosthetic material, cellulitis and thrombosis in one patient each [PROS EPIK-P1-CSR-Table 14.1-4.8].

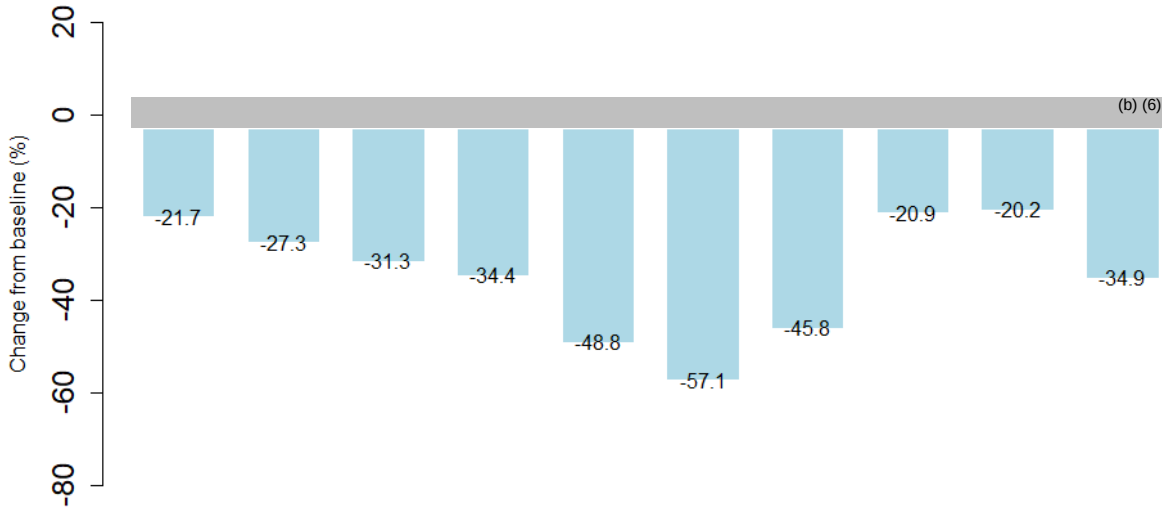
Six adult patients (33.3%) were hospitalized for any reason while on treatment (median duration of treatment - 24 months), of them four patients were hospitalized due to PROS. Reason for hospitalization included: surgery, cellulitis, thrombosis, and colonic volvulus were reported in one patient each [PROS EPIK-P1-CSR-Table 14.3-6.1].

The FDA's Assessment:

The FDA agrees with the analysis of the percent change of sum of target lesion volume (mL) from baseline at Week 24 for all patients. As mentioned previously, only confirmed responses will be considered and the waterfall plot of percent change of lesion size reduction from baseline among responders is included in Figure 10. The FDA did not confirm analysis of patient reported outcome (PRO) or clinical outcome assessment (COA) endpoints. These endpoints are not interpretable due to the study design, as there was no pre-specified plan to administer and interpret the instruments that measure these outcomes. Additionally, the FDA considers the

Applicant's analysis of change in type of medication, non-drug therapies, and HRU to be descriptive and exploratory, and did not confirm this analysis. See the FDA's Assessment of the section "Efficacy Results – Secondary or exploratory COA (PRO) endpoints" below for more details.

Figure 10: Waterfall plot of percent change lesion size reduction from baseline among responders



Dose/Dose Response

Data and The Applicant's Position:

The dose in the majority of the pediatric patients was 50 mg and was 250 mg in adult patients. No dose-response analysis was performed in EPIK-P1.

The FDA's Assessment:

The FDA agrees and has no further comment.

Durability of Response

Data:

Table 24: Summary of duration of response by age category (Efficacy population)

	Pediatric patients (<18 years) N=7 n (%)	Adult patients (>=18 years) N=5 n (%)	All patients N=12 n (%)
n/N (%)	0/7 (0.0)	0/5 (0.0)	0/12 (0.0)
Maximum follow-up (weeks)	129.1	186.7	186.7
Median follow-up (weeks)	92.1	3.9	63.3
Median time to censoring (weeks)	92.1	3.9	63.3
Percentiles (95% CI)			
25th	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
50th	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
75th	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
% Distribution of duration of response (95% CI)			
12 weeks	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
24 weeks	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
36 weeks	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
52 weeks	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)

Response is defined by achieving at least 20% reduction from index date in the sum of measurable target lesion volume provided that none of the individual target lesions have >= 20% increase and in absence of progression of non-target lesions and without new lesions. Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). Distribution of duration of response estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.

In DOR, the start date is the date of first documented response, and the end date is defined as the date of disease progression or death due to any cause.

Source: EPIK-P1-CSR-Table 14.2-2.5

The Applicant's Position:

The median DOR was not estimable as no events (i.e., progressions or deaths) were observed at the cut-off date (Table 23). Treatment with alpelisib should continue for as long as clinical benefit is evident, or until unacceptable toxicity occurs.

Long term efficacy data are expected from the following 2 Phase II studies:
EPIK-P2, Study CBYL719F12201: A prospective clinical Phase II study in patients 2 years and older with PROS. It is a multi-center study with an upfront 16-week, randomized, double-blind,

placebo-controlled period, and extension periods at least 5 years to assess the efficacy, safety and PK of alpelisib in pediatric and adult participants with PROS. The study is ongoing.

EPIK-P3, Study CBYL719F12401: A Phase II multi-center, interventional open label study in pediatric and adult participants with severe or life-threatening complications of PROS who previously participated in EPIK-P1 and who continued to receive treatment with alpelisib after the EPIK-P1 cut-off date (i.e., 09-Mar-2020). The First Patient First Visit is expected in Q4 of 2021.

The FDA's Assessment:
The median duration of response was not reached in the primary efficacy population or in any of the subgroup populations in Table 20. The estimation of duration of response is limited to 10 confirmed responders in the efficacy population, which limits interpretation of the durability of response. Of these 10 responders, 6 (60%) had at least 1 year of response observed. See Table 19 for additional information. The FDA has issued a postmarketing requirement and postmarketing commitment to submit long-term efficacy data from the EPIK-P2 and EPIK-P3 studies, respectively and further describe the duration of the response.

Persistence of Effect

Data and Applicant's Position:

No data are available after treatment is stopped or withheld with alpelisib.

The FDA's Assessment:

The FDA agrees.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data and The Applicant's Position:
There were no PROs collected in EPIK-1.

The FDA's Assessment:

A clinical outcome assessment (COA) is a measure that describes or reflects how a patient feels, functions, or survives. Types of COAs include patient-reported outcome (PRO) measures, observer-reported outcome measures, clinician-reported outcome (ClinRo) measures, and performance outcome measures.

As noted in the EPIK-P1 study protocol, secondary endpoints were selected to support the clinical risk:benefit assessment of alpelisib and to supplement the analysis of the primary endpoint. These secondary endpoints included change in PROS symptoms and complications over time and change in functional status. In the earlier section "Efficacy Results – Secondary and other relevant endpoints," the Applicant states that the five most frequent PROS-related signs and/or symptoms reported at the index date were fatigue, vascular malformations, disseminated intravascular coagulation, limb asymmetry and pain. With the exception of pain, these data, including severity, were per physician report and abstracted from the medical chart. Similarly, changes in functional status including performance status (ECOG, Karnofsky, Lansky) and work/school/pre-school attendance were derived from clinician reported data in the medical chart.

Per the Applicant, pain was assessed as a composite endpoint at Week 24 since pain or its management were not consistently reported across patients and some data points were missing (e.g., start or end date), complicating the evaluation of pain over time. Pain reduction was noted if improvement, relative to the index date, was reported for at least one of the following items (provided that none of the other items was associated with a deterioration during the same period):

- Pain score from a questionnaire recording pain severity (i.e., Wong Baker, FLACC and numerical scale rating) completed by the patient
    - *Of note, a questionnaire recording pain severity was collected for only 11 (six pediatric and five adult patients) of 57 patients*
- Number of concomitant pain medications (excluding opioids)
- Number of opioids
- Number and severity of pain-related medical conditions/treatment emergent adverse events

Given the retrospective nature of data collection in EPIK-P1 single-arm clinical study, the primarily clinician-reported results and the limitations of missing data, analyses of these secondary endpoints are considered descriptive and exploratory. Well-supported claims regarding the effect of alpelisib on changes in PROS signs/symptoms, complications and functional status cannot be made based on the data provided in the submission.

Additional Analyses Conducted on the Individual Trial

Data and The Applicant's Position:
No additional analyses were conducted other than presented in sections above.

The FDA's Assessment:

The FDA also reviewed individual case narratives for all 57 patients in EPIK-P1 that were compiled by the Applicant based on information recorded in the patients' medical charts and reported in the eCRF. Each treating physician was asked to review the data qualitatively and provide a personal assessment of the clinical outcome of the treatment with alpelisib for each patient.

These narratives were submitted in the EPIK-P1 Clinical Study Report and provided detailed information regarding each patient's baseline disease characteristics (including PROS subtype, mutation type, PROS-related medical history and treatment); radiological assessment of target/non-target lesions and response determination as per blinded independent central review; physician assessment of the patient's medical history and condition at baseline (including historical condition, PROS lesions identified, and rationale for alpelisib treatment); the patient's response to alpelisib, including descriptions of changes in symptoms, function, or medical condition; and the Applicant's overall risk:benefit conclusion.

A summary of patient narratives for the 10 confirmed radiologic responders in the efficacy subset is provided in Table 25.

Although all radiologic responders in EPIK-P1 had the CLOVES subtype and harbored a "frequent" PIK3CA mutation, individual case narratives documented early signals that alpelisib exerts a treatment effect in patients with PROS subtypes other than CLOVES and in patients with "less frequent" PIK3CA mutations (Table 26). Some notable findings supportive of clinical response (i.e., amelioration of PROS-related signs and symptoms) to alpelisib in this subgroup include improvements in fatigue, pain, swelling, bleeding, inflammatory flares, ocular function, and mobility. Additionally, the majority of patients in the safety population with a non-PROS diagnosis and/or "less frequent" PIK3CA mutation who were not evaluable for efficacy demonstrated similar signals of clinical response that were reported by the treating physician.

Also of note, although all radiologic responders in EPIK-P1 had the CLOVES subtype and harbored a "frequent" PIK3CA mutation, 10 patients with a PROS diagnosis other than CLOVES and/or a PIK3CA mutation classified as "less frequent" were not evaluable for efficacy due to limitations in imaging (either not obtained at key points or excluding target lesion[s]) that precluded eligibility for the efficacy population. These patients were diagnosed with MCAP, KTS or combination CLOVES/MCAP. As such and due to the overall small sample size, it is difficult to determine the true radiologic response rate in patients with a non-CLOVES subtype; however, clinical improvements were reported in nearly all of these patients.

The FDA acknowledges that the case narratives have certain limitations (e.g., data was retrospectively ascertained for review, patient symptoms such as pain and fatigue were subjective and reported by the treating physician, etc.); however, review of these narratives

provide clinical documentation that provides some preliminary information suggesting that the responses to alpelisib may be clinically meaningful and that patients demonstrating lesion shrinkage, even if not meeting the pre-defined threshold of 20% volumetric reduction for response, may potentially benefit.

To further understand the treatment effect of alpelisib across the genotypic and phenotypic variability observed in PROS, the FDA has issued a postmarketing requirement to verify and describe the clinical benefit of alpelisib in patients with PROS including those who have the non-CLOVES subtype and "less frequent" PIK3CA mutation type.

Table 25: Narrative Summary of Disease Manifestations and Clinical Improvements in Confirmed Responders in EPIK-P1

Patient ID	Age	Sex	PROS Subtype	PIK3CA Mutation/ Category	Summary of Major Disease Manifestations	% Volume Reduction at Week 24	DOR at DCO	Reported Clinical Improvement
(b) (6)	27	M	CLOVES	H1047R/ Frequent	Multiple large vascular malformations affecting chest, abdomen, pelvis and back; congestive heart failure with high output; renal dysfunction with chronic proteinuria; severe scoliosis; paraplegia; left leg overgrowth; chronic DIC; DVT; saddle anesthesia, spastic bladder	22%	43 mo	Improved heart function, scoliosis, saddle anesthesia; reduction in dyspnea, edema, fatigue; stabilized renal function with reduction in chronic proteinuria; improved DIC markers; esthetic changes (visible reduction in volume of overgrowths)
	12	F	CLOVES	H1047R/ Frequent	Asymmetric overgrowth of legs; voluminous splenomegaly; chronic bleeding of vascular malformations; pain; edema; recurrent cellulitis; DIC	27%	30 mo	Reduction in volume of both legs and in splenomegaly, improvement in fatigue and pain, discontinuation of chronic bleeding, no additional blood transfusions required, improved DIC markers
	15	M	CLOVES	H1047L/ Frequent	Mixed lipomatous and vascular malformations of the back, chest and abdomen; pain, fatigue; scoliosis; DIC	31%	18 mo	Improvement in scoliosis, reduction in pain and fatigue, improvement in baseline deformity, patient able to engage in sports
	10	F	CLOVES	E542K/ Frequent	Voluminous lipomatosis infiltration of the back, asymmetric overgrowth of left leg, intrabdominal lipoma, vascular malformation of chest, tethered spinal cord syndrome,	34%	21 mo	Improvement in fatigue, partial correction in scoliosis, esthetic changes noted with volume reduction of back and left leg malformation

					scoliosis, pain, chronic obstructive ventilatory disorder			
(b) (6)	14	M	CLOVES	E542K/ Frequent	Vascular malformation of pelvis, vascular malformation of left buttock/thigh/popliteal fossa and perineum, pain requiring opioids, fatigue, impaired mobility, chronic hematuria, rectal hemorrhage, anal incontinence	48%	28 mo	Resolution of pain, fatigue, hematuria, rectal hemorrhage; discontinuation of opioid medications; able to stand and walk; able to sit for prolonged period and attend school; improved inflammatory markers and DIC; no hospitalizations during treatment period
	5	F	CLOVES	E542K/ Frequent	Lymphatic malformations of the right side associated with inflammatory flares; lymphatic leakage of right arm and chest; voluminous vascular malformations of right arm; cystic lymphangioma in neck associated with bleeding; fatigue;	57%	21 mo	Resolution of swelling, chronic bleeding, pain and inflammatory flares; improvement in fatigue; return of function of right arm permitting various activities (e.g., swimming, bicycling); return to school; correction of visible esthetic & morphological change
	19	F	CLOVES	E545K/ Frequent	Vascular malformation of pelvis, gastrointestinal system and right leg; swelling associated with vascular malformations; severe peripheral neuropathy; severe muscle weakness; flaccid tetraplegia; gastrointestinal bleeding; bladder paralysis; fatigue; pain; chronic DIC	57%	11 mo	Resolution of gastrointestinal bleeding, superficial swelling/bleeding; improvement in pain, fatigue; partial recovery of neuropathy; improved bladder paralysis enabling removal of suprapubic catheter; able to move legs and feet, walk few steps without assistance; returned to school
	38	M	CLOVES	C420R/ Frequent	Voluminous vascular malformations of thorax and abdomen, swelling & bleeding of abdominal vascular malformation, asymmetric overgrowth of legs, disseminated superficial vascular anomalies,	21%	26 d	Resolution of pain, bleeding, swelling, inflammatory flares; healing of abdominal skin ulceration; improvement in fatigue and DIC; 15 kg weight loss associated with reduction of vascular

					bilateral macrodactyly (fingers), chronic DIC, DVT, cellulitis, inflammatory flares, fatigue, pain, impaired mobility			malformations; significant esthetic and morphological changes
(b) (6)	3	F	CLOVES	E545K/ Frequent	Left lower limb overgrowth, superficial lymphatic malformation of abdomen and left knee, vascular malformation of left foot, coagulopathy, anemia	20%	5.6 mo	Baseline symptoms and complications relating to PROS unchanged
	16	F	CLOVES	H1047L/ Frequent	Spinal arteriovenous malformation associated with spinal cord compromise, lipomatous overgrowth, scoliosis, left arm paralysis, right arm numbness and tingling, bilateral leg weakness, leg numbness, back pain	35%	2.8 mo	Resolution of numbness and tingling of right arm

Table 26: Narrative Summary of Disease Manifestations and Clinical Improvements in Patients with PROS Subtype other than CLOVES and Less Frequent PIK3CA mutation in Efficacy Subset of EPIK-P1

Patient ID	Age	Sex	PROS Subtype	PIK3CA Mutation/ Category	Summary of Major Disease Manifestations	% Volume Change at Week 24	Reported Clinical Improvement
(b) (6)	5	F	FIL[a]	H1047R / Less Frequent	Severe infiltrating lipomatosis of left part of face, left parotid gland; facial and tongue asymmetry; facial pain, swelling; fatigue; maxillary hypoplasia	9% reduction	Able to reopen left eye; reduction in asymmetry of tongue and lip; esthetic and morphological changes; reduction in fatigue, pain, and swelling
	15	F	CLOVES[b]/MCAP[c]	E726K/ Less frequent	Diffuse subcutaneous lipomatosis infiltration, megalencephaly, right facial overgrowth, bilateral asymmetric overgrowth of limbs, myopathy, developmental delay, scoliosis, intracerebral venous malformation, hemorrhagic stroke, difficulty walking, bilateral periorbital and palpebral inflammation requiring steroid treatment, retinitis, chemosis,	4% reduction	Reduction in pain, fatigue; able to reopen the eyes; improvement in retinitis (discontinued steroid treatment); resolution of photophobia; able to resume normal activities and socialize again; improvement in scoliosis; improved cognition and behavior; increased muscle strength
	14	F	Mixed vascular malformations	E542K/ Frequent	Severe voluminous mixed lymphatic and venous malformations of the right part of the face involving the right eye, tongue, oral cavity, pharynx and brain; inflammatory flares of vascular malformations,	5% increase	Resolution of pain, fatigue, bleeding; reduction of inflammatory flares permitting discontinuation of steroid treatment; significant esthetic changes due to visible reduction in volume of face and supraorbital & tongue malformations; resolution of lymphatic blebs and venous

							malformations of face and tongue; no longer hiding face with scarf
(b) (6)	3	M	MCAP[c]	Q546R/ Less frequent	Diffuse capillary malformations, truncal lymphatic malformations and lipomatous overgrowth, megalencephaly, polymicrogyria, seizures, global hypotonia, developmental delay, facial asymmetry, pain, inflammatory flares of lymphatic malformations, left homonymous hemianopia, retinal hemangioma and astrocytoma	15% increase	Reduction in pain, fatigue, inflammatory flares; esthetic changes; increased muscle strength; partial recovery of hypotonia; improvement in activities (sitting, standing with help, etc.); reduction in anti-epileptic dose; improvement in eye complications (retinal exudation, leakage) and successful treatment of amblyopia
	9	F	FIL[a]	C420R/ Frequent	Congenital infiltrating lipomatosis of the face, oral hamartomas, hypertrophy of lips, macroglossia, overgrowth of left eyelid, facial asymmetry. superficial vascular malformations of extremities, chronic DIC, fatigue, recurrent inflammatory flares	2% increase	Reduction in fatigue and chronic DIC, significant esthetic improvement
	3	F	CLOVES[b]/MCAP[c]	T1025A/ Less frequent	Hemimegalencephaly, overgrowth of face and arms, disseminated lipomas and superficial vascular malformations, facial asymmetry, bilateral syndactyly of feet, bilateral vascular anomalies of retina, global hypotonia, fatigue	3% reduction	Reduction in fatigue, major esthetic changes, improvement in color and size of vascular anomalies, enhanced cognitive function and behavior with greater social interaction
	10	M	KTS[d]	E110DEL/ Less frequent	Severe left leg and foot hypertrophy with vascular involvement, angiomas on external	Not reported (No assessment	Baseline symptoms/complications related to PROS remained unchanged. Treatment with

					surface of thigh and calf, left leg pain, superficial venous dilatation of left leg	done by BIRC due to lack of target lesion imaging at Week 24)	alpelisib was not associated with any changes in patient's quality of life.
(b) (6)	7	M	FIL[a]	C420R/ Frequent	Right facial hypertrophy, hemimegalencephaly, epilepsy, anisometropia, mild left hemiparesis	2% increase	Improved quality of life with decreased seizure activity (seizure-free for 10 months at time of data cutoff)

[a]FIL: Facial infiltrating lipomatosis
[b]CLOVES: Congenital lipomatous overgrowth, vascular malformation, epidermal nevi and skeletal anomalies
[c]MCAP: Megalencephaly-capillary malformation
[d]KTS: Klippel-Trenaunay syndrome

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
Refer to section 8.1.5 (*Integrated Assessment of Effectiveness*) for evaluation of efficacy in EPIK-P1, a single-arm clinical study of patients 2 years of age and older with severe or life-threatening PROS necessitating treatment as per their treating physician and who were enrolled in an expanded access program to receive alpelisib for compassionate use.

8.1.4. Assessment of Efficacy Across Trials

Data and The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.1.5. Integrated Assessment of Effectiveness

Data and The Applicant's Position:

Results from EPIK-P1 provide substantial evidence of meaningful clinical benefit of alpelisib for the treatment of adult and pediatric patients aged ≥ 2 years of age with PROS. Targeting the underlying cause of the disease (mutation in the PIK3CA gene) offers a meaningful clinical benefit to PROS patients such as a shrinkage or a stabilization of PROS lesions, an improvement in signs and symptoms associated with the disease as well as the patient's general condition.

Key Benefits

The key benefits in patients with PROS as demonstrated in EPIK-P1 are:

a. Reduction in lesion volume as evident from the significant proportion of patients achieving response at Week 24 and reduction in the sum of measurable lesion volume overtime (and no further disease progression or death).
b. Improvement in PROS related signs and symptoms including improvement in pain, irrespective of whether the patient was considered a responder, non-responder, or had missing assessment.
c. No patients requiring rescue surgery by Week 24 due to disease progression.
d. Improvement in performance status.

Efficacy (complete case analysis, N=32)

a) The reduction in lesion volume is demonstrated by the results of the analysis of the primary endpoint and is supported by sustained reduction in the sum of target lesion volume (Table 16).

- The robustness of the results was confirmed by additional subgroup and sensitivity analyses (Table 16 and Table 17).

- Marked reductions in lesion volume were evident as early as the initial 12 weeks of therapy and were sustained and/or improved at subsequent time points while on treatment (Table 20).
- The median DOR was not estimable as there were no progressions or deaths in any of the responders (Table 23).
- Of patients who had a radiological assessment at Week 24, none had progression of their disease at this time point indicating a 100% disease control rate (response, non-response/non progression) at Week 24.

Of note, all patients considered as non-responders based on the primary efficacy endpoint, except one patient who discontinued due to lack of efficacy, reported a clinical benefit and none of these patients had radiologically confirmed disease progression. A reduction in the target lesion volume of non-responders was observed as early as Week 4 and remained stable over time.

Clinical benefit (all 57 patients)

b) There was clear evidence of clinically meaningful improvement in PROS signs and symptoms associated with alpelisib treatment in the intended population.

- Treatment with alpelisib reduced clinical co-morbidity factors and improved disease-related signs and symptoms across the Full study population (n=57). These signs and symptoms showed early improvement at Week 12, which were confirmed at Week 24 and subsequently sustained and/or improved over time (Table 21).
    - Improvement in pain: A marked reduction in grade 3 pain was reported in all patients over time (Figure 8).

c) No patient required rescue surgery by Week 24 due to disease progression, thus reducing the burden of surgery and expected co-morbidities (Keppler-Noreuil et al 2014). Two pediatric patients had surgery due to clinical disease progression (not radiologically confirmed) after Week 24, however these patients continued treatment with alpelisib as they were deriving clinical benefit from the treatment of alpelisib.

d) Treatment with alpelisib was associated with improvement in functional status at Week 24 including improved performance status (ECOG, Lansky, Karnofsky score) (Table 22). The improvement in the score was sustained at Week 52 and end of study (Table 22 and Figure 9).

The efficacy results, including meaningful clinical benefit, observed in this retrospective, real world study, were consistent in both pediatric patients and adult patients and support the indication proposed.

The following limitations were noted:

• Since this was a non-interventional study and due to retrospective nature of collecting data, efficacy and safety assessments were performed as per the local standard of care. This led to a number of missing imaging scans at baseline and at Week 24 and hence 25/57 (43.9%) of patients did not have a response assessment at Week 24.

- This was not a controlled but an observational study. There was not a pre-planned visit schedule. This implied that assessments including the mobility and pain severity questionnaire, cardiac imaging, and ECG parameters were neither collected in a consistent way nor assessed for the majority of the patients. This did not enable their evaluation in the context of this study in a meaningful way.
- Laboratory tests were performed according to local practice and were done less frequently compared to a prospective study. Although this is a limitation, there was no major issue detected.
- Start and/or end dates were frequently reported partially or completely missing. To enable association of an event to a specific period, pre-specified imputation rules were applied. As a conservative approach, if an event was reported with both start and end dates completely missing or for events with an unknown start date but with an end date with in the study period, the event was assumed to occur during the study period. This has impacted particularly the reporting of the medication, the non drug therapies and the definition of treatment emergent AE.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position with the following key exceptions:

- While signals of clinical benefit were seen, as would be expected with response rate as reasonably likely to predict clinical benefit, FDA does not consider meaningful clinical benefit to have been demonstrated. Rather FDA considers that response rate is a surrogate endpoint reasonably likely to predict clinical benefit. Confirmation of benefit will be obtained in post-marketing trials.
- As previously described, the FDA considers the response rate to be 27% (95% CI: 14, 44) based on 10 confirmed responders in the efficacy population of 37 patients (see Section 8.1.2 "Study Results"). All results from other populations and using other response endpoints (e.g., unconfirmed response) are considered sensitivity and supportive analyses.
- As noted in subsection "Efficacy Results – Secondary or exploratory COA (PRO) endpoints", given the retrospective nature of data collection in the EPIK-P1 single-arm clinical study, the primarily clinician-reported results, and the limitations of missing data, well-supported claims regarding the effect of alpelisib on changes in PROS

signs/symptoms, complications, use of supportive medications and non-drug interventions (e.g., surgery) to treat complications of PROS, and functional status cannot be made based on the data provided in the NDA. Although supportive of the primary endpoint, analyses of these secondary endpoints are considered descriptive and exploratory.

The response rate determined by blinded independent central review and the durability of responses, including 60% of patients with a response lasting at least one year, observed in EPIK-P1 are considered persuasive in the setting of a disease with a high unmet medical need and where lesions are not expected to shrink without intervention. As PROS is a lifelong disease that will likely require chronic treatment, additional information, including extended follow-up to assess duration of response and systematically collected data regarding long-term patient outcomes, is needed to verify that treatment with alpelisib provides a clinical benefit to patients. Additional information and precision on response rate data will also be obtained. Information derived from the ongoing EPIK-P2 trial, which will be submitted to fulfill the PMR required under Subpart H, will provide the information needed to verify the clinical benefit of alpelisib in patients with severe manifestations of PROS and further elucidate the consistency of the treatment effect of alpelisib in this genotypically and phenotypically heterogeneous disease in a randomized setting.

8.2. **Review of Safety**

Data and The Applicant's Position:
A comprehensive assessment of safety data relevant to the use of alpelisib as monotherapy in patients with PROS is provided in the subsequent sections below (Section 8.2.4).
Given the rarity of the spectrum of diseases that were studied, data from EPIK-P1 are considered appropriate to assess the safety of alpelisib in the target population. The safety data from EPIK-P1 are presented for the overall population, and also separately for pediatric and adult patients with PROS.

Overall, the safety profile of alpelisib in pediatric and adult patients with PROS is consistent with the mechanism of action of alpelisib and compares favorably to the known safety profile characterized in adult patients in the oncology setting.

The FDA's Assessment:
Overall, the FDA agrees with the Applicant's position. Please see Section 8.2.1 for additional discussion.

8.2.1. Safety Review Approach

Data and The Applicant's Position:

This safety evaluation of alpelisib in patients with PROS, administered as a monotherapy, is primarily based on the 57 patients treated in EPIK-P1. To provide further context for the interpretation of the safety profile of alpelisib administered as monotherapy, reference is made to the Piqray NDA for the safety data from two dose-finding studies X2101 and X1101 in 167 adult patients with solid tumors (134 additional adult patients with advanced solid malignancies who were treated in Study X2101 and 33 other exclusively Japanese patients treated in Study X1101) (Refer to Section 7.1 for details of the clinical studies provided). Data from these studies allow for an informed assessment of the safety profile of single agent alpelisib and an evaluation of the overall benefit-risk in subjects with PROS.

The safety data were not pooled across studies due to the significant difference in study indications, populations (e.g. a majority of pediatric patients in EPIK-P1 vs exclusively adult patient in the oncology studies), wide range of alpelisib dose levels (30 mg to 400 mg/day), administration schedules (once and twice-daily dosing) and regimens (single agent and combination with fulvestrant) used in the studies.

The safety profile of alpelisib has been extensively characterized during the development of treatment for postmenopausal women, and men, with HR-positive, HER2-negative, advanced/locally advanced or metastatic breast cancer with a PIK3CA mutation. The pivotal clinical Study BYL719C2301 (SOLAR-1) provided the safety data of treatment combination of alpelisib 300 mg q.d. with fulvestrant 500 mg i.m compared with patients receiving combination of placebo and fulvestrant. The median duration of exposure of alpelisib plus fulvestrant treatment arm was 8.2 months. The safety profile is described in the Piqray® USPI.

AE categories expected to be associated with alpelisib, as pre-identified during the development program, were analyzed. These adverse events of special interest (AESIs) were selected based on the mechanism of action of alpelisib coupled with biological plausibility, as well as nonclinical observations and the clinical experience in the oncology setting.

Serious adverse events and deaths reported in the Novartis Global Safety Database (Argus) from compassionate use programs for PROS patients are provided up to 28-Feb-2021 as line-listing narratives and via a tabular summary (i.e. CBYL719F12001M [MAP in PROS patients], CBYL719XFR01I [ATU in PROS patients in France], and CBYL719X2001I (PROS patients only).

The post-marketing experience with alpelisib in the oncology setting as well as the compassionate use in PROS patients are also reviewed on an ongoing basis and results are included in the Periodic Safety Update Reports (PSURs). Additionally, published information on the safety of alpelisib (both nonclinical and clinical) is evaluated on an ongoing basis.

Overall, this approach is considered appropriate for the detection and characterization of common AEs and to provide guidance on adverse event management for patients with PROS.

The FDA's Assessment:

The primary source of safety data in this NDA is EPIK-P1, a single-arm clinical study which enrolled 57 adult and pediatric patients who received alpelisib via an expanded access program for compassionate use, and comprised the overall safety population. All patients received at least one dose of alpelisib a minimum of 24 weeks prior to an established data cutoff of March 9, 2020, and met key inclusion criteria including 1) a confirmed diagnosis of PROS & documented PIK3CA mutation, 2) severe or life threatening disease requiring treatment as assessed by the treating physician, and 3) had available medical chart history.

The safety data from EPIK-P1 was also supported by the Applicant's analysis of a global safety database (Argus) to retrieve all serious adverse event (SAE) reports associated with alpelisib use for PROS. The Applicant conducted a cumulative search of Argus through February 28, 2021 and compiled a summary report that was presented in an appendix to the Clinical Overview.

The review of safety included analysis of the submitted clinical study report, datasets, line listings, electronic case report forms and case narratives from EPIK-P1. Additionally, reports of SAEs and adverse events of special interest (AESI) were also reviewed. The analytical tools used included JMP and MAED.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 27: Duration of exposure to alpelisib by age category - EPIK-P1 (Full study population)

	2-5 years N=11	6-11 years N=12	12-17 years N=16	Pediatric patients (<18 years) N=39	Adult patients (>=18 years) N=18	All patients N=57
Duration of exposure (months)						
Mean (SD)	23.1 (9.83)	21.0 (14.47)	22.7 (11.60)	22.3 (11.83)	21.3 (11.16)	22.0 (11.53)
Median	18.1	13.6	19.0	18.0	19.2	18.1
Q1-Q3	15.5 - 35.8	9.5 - 35.8	15.2 - 36.1	13.5 - 35.8	13.9 - 20.5	13.6 - 35.8
Min-Max	11.5 - 36.6	4.5 - 41.8	3.4 - 36.6	3.4 - 41.8	8.0 - 49.9	3.4 - 49.9
Duration of exposure categories-n (%)						
<6 months	0	2 (16.7)	1 (6.3)	3 (7.7)	0	3 (5.3)
6-<12 months	1 (9.1)	3 (25.0)	2 (12.5)	6 (15.4)	3 (16.7)	9 (15.8)
12-<24 months	6 (54.5)	2 (16.7)	7 (43.8)	15 (38.5)	11 (61.1)	26 (45.6)
24-<36 months	3 (27.3)	4 (33.3)	2 (12.5)	9 (23.1)	1 (5.6)	10 (17.5)

	2-5 years N=11	6-11 years N=12	12-17 years N=16	Pediatric patients (<18 years) N=39	Adult patients (>=18 years) N=18	All patients N=57
36-<48 months	1 (9.1)	1 (8.3)	4 (25.0)	6 (15.4)	2 (11.1)	8 (14.0)
48-<60 months	0	0	0	0	1 (5.6)	1 (1.8)

Duration of exposure (months) = ((last date of know exposure to alpelisib) – (index date) + 1)/ 30.4375
Source: EPIK-P1-CSR-Table 14.3-1.1

The Applicant's Position:
Exposure to study treatment in EPIK-P1 was considered appropriate to allow for an adequate assessment of safety in patients who are representative of the intended target population (Table 27).

The FDA's Assessment:
The FDA agrees with the overall exposure data presented in Table 27 and the position that the safety database from EPIK-P1 provides an adequate assessment of safety in adult and pediatric patients with PROS to support the safety of alpelisib in patients 2 years of age and older with severe manifestations of PROS. Given the limited sample size, retrospective nature of safety data collection, potential variability in the approach to safety monitoring taken by individual clinicians responsible for treating patients in the expanded access program, and extension of the indication to pediatric patients 2 years of age and older, the FDA has issued a postmarketing requirement to conduct safety analyses from clinical studies that further characterize the potential serious risk of long-term adverse effects on growth and development in pediatric patients. Additionally, as alpelisib is intended for chronic use in patients with PROS, the FDA considers evaluation of the safety of long-term administration to be a priority in further development of alpelisib for this target population.

Relevant characteristics of the safety population:

Data:
Please refer to Table 12 and Table 14 (demographics and disease history in Section 8.1.2).

The Applicant's Position:
A broad/heterogeneous population including pediatric and adult patients with PROS was enrolled. The demographics, underlying phenotypes, PIK3CA mutations and other baseline characteristics are representative of the intended patient population and allow the resultant data to be extrapolated to all patients with the proposed indication.

The FDA's Assessment:
The FDA generally agrees with the Applicant's position that a heterogeneous population of adult and pediatric patients with PROS was enrolled in EPIK-P1 and that the overall demographics and disease characteristics of the safety population permit sufficient assessment of safety in the proposed indication.

Adequacy of the safety database:

Data and The Applicant's Position:
The safety profile for the indication being sought is determined primarily from EPIK-P1 (N = 57). Despite a relatively modest sample size, the studied population is considered to adequately represent the population with this rare disease. The demographics, underlying phenotypes and PIK3CA-mutations, and other baseline characteristics are representative of the intended patient population and allow the resultant data to be extrapolated to all patients with the proposed indication.

Beyond the EPIK-P1 pivotal registration study, the safety analyses focused on 167 patients receiving alpelisib monotherapy at higher dose in Studies X2101 and X1101; results from these respective datasets were consistent with those reported from EPIK-P1 for adult patients.

Also, the safety profile of alpelisib has been extensively characterized during the development of treatment for postmenopausal women, and men, with HR-positive, HER2-negative, advanced/locally advanced or metastatic breast cancer with a PIK3CA mutation. The pivotal clinical, SOLAR-1, provided the safety data of treatment combination of alpelisib 300 mg q.d. with fulvestrant 500 mg i.m compared with patients receiving combination of placebo and fulvestrant. The median duration of exposure of alpelisib plus fulvestrant treatment arm was 8.2 months. The safety profile is described in the Piqray® USPI. The analysis also takes into account safety data reported to the Novartis Global Safety Database (Argus) from the PROS compassionate use programs under which 193 patients (including 121 pediatric and 72 adult) received treatment across 17 countries (as of 28-Feb-2021).

The FDA's Assessment:
The primary safety data from EPIK-P1, the supportive extensive safety database in adult patients with cancer treated with alpelisib, and the supplemental data from the Applicant's interrogation of the Argus database submitted in the application allowed for an informed risk assessment of alpelisib in the intended indication. As noted in section 8.2.2, the longer-term safety profile of alpelisib in pediatric patients with PROS requires further evaluation in the post-marketing setting.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data and The Applicant's Position:
No meaningful concerns were identified in the quality and integrity of the submitted datasets and individual case narratives.

The FDA's Assessment:
The FDA agrees with the Applicant's position. The NDA submission contains all required components of the electronic common technical document (eCTD). See Section 8.1.12 "Data Quality and Integrity" for the FDA's assessment of overall data quality and integrity in the NDA. Further, refer to section 4.1 "Office of Scientific Investigation" for a summary of clinical site inspections.

Categorization of Adverse Event

Data and The Applicant's Position:

The safety of study treatment was evaluated on the basis of the:

- Frequency, type, severity, and causal relationship with study treatment of treatment-emergent AEs.
  - AEs and laboratory parameters were graded using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 in EPIK-P1, Version 4.03 in Study X2101 and Version 4.0 in Study X1101.
- Frequency of deaths, SAEs, and other clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose interruption and/or reduction).
- Changes in laboratory variables, with particular attention to grade 3/4 abnormalities.

As a conservative approach, the AEs reported with missing start and end dates or missing start date with end date reported in the study period were assumed to be reported during the study period (i.e. treatment-emergent AEs).

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 for EPIK-P1, Version 18.1 for Study X1101, and Version 17.1 for Study X2101.

The FDA's Assessment:
The FDA agrees with the general methods used for the assessment of safety and tolerability of alpelisib. The FDA acknowledges that the Applicant used a conservative approach to reporting of adverse events such that adverse events with missing start and end date, or missing start date with end date reported in the study period, were assumed to have occurred during the study period and classified as treatment-emergent events.

Additionally, the Applicant considered the following to be adverse events of special interest (AESI) based on mechanism of action of alpelisib, biological plausibility and the clinical experience in the oncology setting: gastrointestinal toxicity (nausea, vomiting, diarrhea), hyperglycemia, hypersensitivity, severe cutaneous reactions, rash, pneumonitis, pancreatitis, and stomatitis.

Routine Clinical Tests

The Applicant's Position:
The laboratory tests in EPIK-P1 were performed according to local practice and as part of the normal laboratory visits. Though these were done less frequently than expected in a prospective study assessing the safety of alpelisib, no major issue was detected.

Overall, the routine clinical and laboratory evaluations performed were adequate to assess the safety of alpelisib in this rare population.

The FDA's Assessment:
The FDA agrees with the Applicant that laboratory studies in EPIK-P1 were performed as per routine clinical practice and not systemically collected according to a set schedule. Despite the inherent limitations of the small sample size and the retrospective collection of data in EPIK-P1, in light of the well-established safety profile of alpelisib including laboratory abnormalities in a larger study population in the oncology setting, the FDA considers the data submitted in the NDA to be sufficient to permit assessment of safety.

8.2.4. Safety Results

This safety evaluation of alpelisib in patients with PROS is primarily based on the 57 patients treated in EPIK-P1 and the results are presented in the sections below.

Deaths

Data and The Applicant's Position:
None of the patients died during study treatment in EPIK-P1.

The FDA's Assessment:
The FDA agrees that as of the data cutoff of March 9, 2020, none of the 57 patients in the safety population had died while receiving alpelisib via expanded access for compassionate use.

Serious Adverse Events

Data:

Table 28: Serious adverse events irrespective of study treatment relationship by preferred term and age category (reported in at least 2 patients in the overall population in all grades) (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (< 18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one event	3 (27.3)	1 (9.1)	2 (16.7)	0	5 (31.3)	2 (12.5)	10 (25.6)	3 (7.7)	11 (61.1)	9 (50.0)	21 (36.8)	12 (21.1)
Cellulitis	0	0	0	0	1 (6.3)	1 (6.3)	1 (2.6)	1 (2.6)	1 (5.6)	1 (5.6)	2 (3.5)	2 (3.5)
Dehydration	0	0	1 (8.3)	0	0	0	1 (2.6)	0	1 (5.6)	1 (5.6)	2 (3.5)	1 (1.8)
Gait disturbance	1 (9.1)	0	1 (8.3)	0	0	0	2 (5.1)	0	0	0	2 (3.5)	0
Pain in extremity	0	0	0	0	0	0	0	0	2 (11.1)	1 (5.6)	2 (3.5)	1 (1.8)
Vascular malformation	1 (9.1)	0	0	0	1 (6.3)	0	2 (5.1)	0	0	0	2 (3.5)	0

A patient with multiple severity grades for an AE is only counted under the maximum grade.

Treatment emergent adverse events- are, PROS and non–PROS related, events starting during the study period (after or on the index date) or starting prior and worsening during the study period.

Adverse events reported are intended as treatment emergent events.

MedDRA version 24.0, CTCAE version 4.03.

Source: EPIK-P1-CSR-Table 14.3.1-1.6

The Applicant's position:

An overview of the most frequently occurring SAEs is provided in Table 28. The majority of SAEs (e.g. cellulitis, gait disturbance, pain in extremity, vascular malformation) were explained by underlying PROS and related co-morbidities. Overall, no unexpected safety concerns have been identified in the PROS population (in 57 patients in spite of the rarity of the disease), including in pediatric patients ranging from 2 to 17 years of age.

Of note, SAEs captured in EPIK-P1 were not entered in the Novartis Global Safety Database as they were reported to Novartis in the context of the MAP/ATU (under which patients were treated with alpelisib) and in accordance with local reporting requirements. A review of SAEs

reported to the Novartis Global Safety Database (Argus) for all ongoing Novartis compassionate use programs was conducted using a data cutoff date of 28-Feb-2021. The review did not identify any new safety concern.

The FDA's Assessment:
The FDA agrees with the serious adverse event (SAE) data presented in Table 28. The rate of SAEs, irrespective of causality, in EPIK-P1 was 37% (SAEs were reported in 21 of 57 patients in the safety population). However, based upon review of SAE reports, the FDA assessed that most of the SAEs that were documented were likely attributable to underlying disease and concluded that overall, serious adverse reactions considered related to the investigational drug occurred in 12% of patients who received alpelisib in EPIK-P1. The FDA does not agree that the event of cellulitis is definitely unrelated to use of alpelisib. Serious adverse reactions occurring in two or more patients included dehydration (n=2) and cellulitis (n=2).

Additionally, review of SAE reports from patients treated with alpelisib for PROS that were submitted to the Argus database and summarized by the Applicant in the NDA did not identify any new or unexpected safety signals.

Dropouts and/or Discontinuations Due to Adverse Effects

Data and The Applicant's position:
No AEs were reported that led to treatment discontinuation in EPIK-P1.

The FDA's Assessment:
The FDA agrees that none of the patients in the safety population permanently discontinued alpelisib due to an adverse event.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 29: Adverse events leading to dose adjustment and/or interruption (any grade >5% or reported by at least 1 patient as grade 3 or higher in the overall population) irrespective of study treatment relationship by preferred term and age category (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (< 18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	0	0	1 (8.3)	0	1 (6.3)	0	2 (5.1)	0	5 (27.8)	2 (11.1)	7 (12.3)	2 (3.5)
Cellulitis	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Impaired healing	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)

A patient with multiple severity grades for an AE is only counted under the maximum grade.
Treatment emergent adverse events- are, PROS and non–PROS related, events starting during the study period (after or on the index date) or starting prior and worsening during the study period.
Adverse events reported are intended as treatment emergent events.
MedDRA version 24.0, CTCAE version 4.03.
Source: EPIK-P1-CSR-Table 14.3.1-1.10

The Applicant's Position:

The most frequently occurring AEs leading to dose adjustment and/or interruption are shown in Table 29. Few patients experienced AEs leading to dose adjustment and/or interruption (7/57 patients; 12.3%). Notably, none of the patients reported grade 3/4 AEs leading to dose reduction, and grade 3 AEs leading to dose interruption occurred in two patients (3.5%): cellulitis and impaired healing (one patient, each).

The FDA's Assessment:

The FDA's analysis of dosage interruptions and dose reductions due to toxicity is shown below in Table 30 and Table 31. The FDA agrees with the Applicant that overall, few patients required dosage interruption or dose reduction and that the majority of adverse events were low grade (Grade 1 or 2).

Dosage interruption due to an adverse reaction occurred in 11% of patients in EPIK-P1. Adverse reactions requiring alpelisib interruption in two or more patients included dizziness (n=2) and vomiting (n=2).

Table 30: Dosage Interruptions due to Adverse Events in EPIK-P1

	Adult Patients (>=18 years) N = 18 N (%)	Pediatric Patients (<18 years) N = 39 N (%)	All Patients N = 57 N (%)
Drug interruption due to AEs	**3 (17)**	**2 (5)**	**6 (11)**
Dizziness	1 (6)	1 (2.6)	2 (3.5)
Vomiting	1 (6)	1 (2.6)	2 (3.5)
Cellulitis	1 (6)	0 (0)	1 (1.7)
Headache	1 (6)	0 (0)	1 (1.7)
Impaired Healing	1 (6)	0 (0)	1 (1.7)
Nausea	1 (6)	0 (0)	1 (1.7)
Urinary Tract Infection	1 (6)	0 (0)	1 (1.7)
Alopecia	1 (6)	0 (0)	1 (1.7)
Acidosis	0 (0)	1 (2.6)	1 (1.7)
Dehydration	0 (0)	1 (2.6)	1 (1.7)
Lethargy	0 (0)	1 (2.6)	1 (1.7)
Viral Infection	0 (0)	1 (2.6)	1 (1.7)

Source: ADSL (Subject-Level Analysis Dataset) - 2021-07-28, ADAE (Adverse Events Analysis Data) - 2021-07-28.
Variables used: USUBJID, AGEGR2, FSPFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

Dose reduction due to an adverse reaction occurred in 5% of patients in EPIK-P1 (Table 31).

Table 31: Dose Reduction due to Adverse Events in EPIK-P1

	Adult Patients (>=18 years) N = 18 N (%)	Pediatric Patients (<18 years) N = 39 N (%)	All Patients N = 57 N (%)
Dose reduction due to AEs	**3 (17)**	**0 (0)**	**3 (5)**
Alopecia	1 (6)	0 (0)	1 (1.7)
Memory Impairment	1 (6)	0 (0)	1 (1.7)
Soft Tissue Infection	1 (6)	0 (0)	1 (1.7)

Source: ADSL (Subject-Level Analysis Dataset) - 2021-07-28, ADAE (Adverse Events Analysis Data) - 2021-07-28.
Variables used: USUBJID, AGEGR2, FSPFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

Significant Adverse Events

The Applicant's Position:
Significant AEs reported in EPIK-P1 are described in the sections above (Table 28). None of the patients died during EPIK-P1 and none of the patients discontinued study treatment due to AEs.

The FDA's Assessment:
Although not all toxicities observed with alpelisib in the oncology setting (i.e., those included in the PIQRAY label) were directly observed in the safety population in EPIK-P1, the significant adverse events of severe hypersensitivity, severe cutaneous adverse reactions, hyperglycemia, and pneumonitis have been included in the *Warnings and Precautions* section of the label. Given the small size of the safety database from EPIK-P1, the lack of observation of these adverse events does not suggest that these events will not occur in patients with PROS, and providers should be informed of these potential toxicities.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 32: Adverse events (any grade >5% or reported by at least 1 patient as grade 3 or higher in the overall population), suspected to be study treatment related by preferred term and age category (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (< 18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	2 (18.2)	0	3 (25.0)	0	4 (25.0)	0	9 (23.1)	0	13 (72.2)	1 (5.6)	22 (38.6)	1 (1.8)
Hyperglycaemia	0	0	0	0	2 (12.5)	0	2 (5.1)	0	5 (27.8)	0	7 (12.3)	0
Aphthous ulcer	1 (9.1)	0	1 (8.3)	0	1 (6.3)	0	3 (7.7)	0	3 (16.7)	0	6 (10.5)	0
Alopecia	0	0	0	0	0	0	0	0	3 (16.7)	0	3 (5.3)	0
Stomatitis	1 (9.1)	0	2 (16.7)	0	0	0	3 (7.7)	0	0	0	3 (5.3)	0
Cellulitis	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (< 18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**

A patient with multiple severity grades for an AE is only counted under the maximum grade.
Treatment emergent adverse events- are, PROS and non–PROS related, events starting during the study period (after or on the index date) or starting prior and worsening during the study period.
Adverse events reported are intended as treatment emergent events.
MedDRA version 24.0, CTCAE version 4.03.
EPIK-P1-CSR-Table 14.3.1-1.2

The Applicant's Position:

The most frequently occurring treatment-related AEs reported in EPIK-P1, including hyperglycemia, stomatitis and alopecia, are known safety risks with alpelisib. None of these AEs had severity grade 3/4. No grade 4 treatment-related AEs were reported. The only grade 3 treatment-related AE was cellulitis, which occurred in an adult patient with a relevant medical history of recurrent soft tissue infections (Table 32).

Laboratory Findings

Data:

Hematology

Table 33: Worst post-index date hematology abnormalities based on CTC grades during the study period by age category (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (<18 years) N=39		Adult patients (≥ 18 years) N=18		All patients N=57	
	All grades n (%)	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Activated partial thromboplastin time, increase	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Fibrinogen, decrease	1 (9.1)	0	0	0	0	0	1 (2.6)	0	1 (5.6)	0	2 (3.5)	0

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (<18 years) N=39		Adult patients (≥ 18 years) N=18		All patients N=57	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Hemoglobin, decrease	5 (45.5)	0	1 (8.3)	1 (8.3)	8 (50.0)	1 (6.3)	14 (35.9)	2 (5.1)	5 (27.8)	1 (5.6)	19 (33.3)	3 (5.3)
Leukocytes, increase	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.6)	1 (2.6)	0	0	1 (1.8)	1 (1.8)
Leukocytes, decrease	7 (63.6)	0	6 (50.0)	0	6 (37.5)	0	19 (48.7)	0	6 (33.3)	0	25 (43.9)	0
Lymphocytes, increase	8 (72.7)	0	2 (16.7)	0	3 (18.8)	0	13 (33.3)	0	1 (5.6)	0	14 (24.6)	0
Lymphocytes, decrease	3 (27.3)	0	3 (25.0)	0	6 (37.5)	0	12 (30.8)	0	1 (5.6)	1 (5.6)	13 (22.8)	1 (1.8)
Neutrophils, decrease	2 (18.2)	0	2 (16.7)	0	5 (31.3)	0	9 (23.1)	0	1 (5.6)	1 (5.6)	10 (17.5)	1 (1.8)
Platelets, decrease	0	0	2 (16.7)	0	5 (31.3)	0	7 (17.9)	0	5 (27.8)	1 (5.6)	12 (21.1)	1 (1.8)

Patients are counted only for the worst grade observed post-index date values. Laboratory assessments performed more than 30 days after last study treatment administration date are not summarized.
Source: EPIK-P1-CSR-Table Table 14.3-7.9

The Applicant's Position

The worst post-index date hematological abnormalities in the Full study population were mostly grade 1 and grade 2, and generally consisted of transient shifts followed by returns to normal values with no alpelisib dose modification. Most of these abnormalities could be explained by underlying or concurrent medical conditions. Of note, no grade 4 events were reported and none of the abnormalities were considered clinically significant (Table 33).

Clinical chemistry

Table 34: Worst post-index date biochemistry abnormalities based on CTC grades during the study period by age category (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (<18 years) N=39		Adult patients (≥ 18 years) N=18		All patients N=57	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Alanine aminotransferase, increase	2 (18.2)	0	3 (25.0)	0	2 (12.5)	0	7 (17.9)	0	3 (16.7)	0	10 (17.5)	0
Albumin, decrease	0	0	1 (8.3)	0	1 (6.3)	0	2 (5.1)	0	4 (22.2)	0	6 (10.5)	0
Alkaline phosphatase, increase	1 (9.1)	0	2 (16.7)	0	0	0	3 (7.7)	0	1 (5.6)	0	4 (7.0)	0
Aspartate aminotransferase, increase	3 (27.3)	0	2 (16.7)	0	5 (31.3)	0	10 (25.6)	0	3 (16.7)	0	13 (22.8)	0
Bilirubin, increase	1 (9.1)	0	2 (16.7)	0	6 (37.5)	0	9 (23.1)	0	8 (44.4)	2 (11.1)	17 (29.8)	2 (3.5)
Calcium corrected, increase	1 (9.1)	0	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Calcium corrected, decrease	5 (45.5)	0	6 (50.0)	0	12 (75.0)	0	23 (59.0)	0	12 (66.7)	0	35 (61.4)	0
Cholesterol, increase	6 (54.5)	0	2 (16.7)	0	4 (25.0)	0	12 (30.8)	0	1 (5.6)	0	13 (22.8)	0
Creatine kinase, increase	5 (45.5)	0	1 (8.3)	0	1 (6.3)	0	7 (17.9)	0	5 (27.8)	0	12 (21.1)	0
Creatinine, increase	8 (72.7)	0	6 (50.0)	0	4 (25.0)	0	18 (46.2)	0	2 (11.1)	0	20 (35.1)	0
Gamma glutamyl transferase, increase	0	0	0	0	1 (6.3)	0	1 (2.6)	0	6 (33.3)	0	7 (12.3)	0
Glucose, increase	0	0	0	0	4 (25.0)	0	4 (10.3)	0	2 (11.1)	1 (5.6)	6 (10.5)	1 (1.8)
Magnesium, increase	2 (18.2)	0	1 (8.3)	0	2 (12.5)	1 (6.3)	5 (12.8)	1 (2.6)	0	0	5 (8.8)	1 (1.8)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (<18 years) N=39		Adult patients (≥ 18 years) N=18		All patients N=57	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Magnesium, decrease	0	0	2 (16.7)	0	6 (37.5)	0	8 (20.5)	0	9 (50.0)	1 (5.6)	17 (29.8)	1 (1.8)
Phosphate, decrease	8 (72.7)	0	9 (75.0)	0	8 (50.0)	0	25 (64.1)	0	10 (55.6)	2 (11.1)	35 (61.4)	2 (3.5)
Potassium, increase	2 (18.2)	0	4 (33.3)	0	4 (25.0)	0	10 (25.6)	0	4 (22.2)	0	14 (24.6)	0
Potassium, decrease	0	0	0	0	2 (12.5)	0	2 (5.1)	0	5 (27.8)	0	7 (12.3)	0
Sodium, increase	0	0	0	0	1 (6.3)	0	1 (2.6)	0	0	0	1 (1.8)	0
Sodium, decrease	1 (9.1)	0	2 (16.7)	0	1 (6.3)	0	4 (10.3)	0	3 (16.7)	1 (5.6)	7 (12.3)	1 (1.8)
Triglycerides, increase	4 (36.4)	0	2 (16.7)	0	2 (12.5)	0	8 (20.5)	0	2 (11.1)	0	10 (17.5)	0
Urate, increase	0	0	3 (25.0)	1 (8.3)	0	0	3 (7.7)	1 (2.6)	4 (22.2)	1 (5.6)	7 (12.3)	2 (3.5)

Patients are counted only for the worst grade observed post-index date values. Laboratory assessments performed more than 30 days after last study treatment administration date are not summarized.
Source: EPIK-P1-CSR-Table 14.3-7.10

The Applicant's Position

The worst post-index date biochemistry abnormalities were mostly grade 1 or 2. The grade 3 biochemistry abnormalities reported were infrequent and none of the abnormalities were considered clinically significant by the investigators. None of the abnormalities were grade 4, except for decreased magnesium in one adult patient which was a result of a data entry issue at the site. In this case, the entered value for magnesium (zero) is implausible and incompatible with life (Table 34).

The FDA's Assessment:

Refer to the FDA's comments in the section following the Applicant's assessment of "Adverse Reaction".

Adverse reaction

Data:

Table 35: Adverse reactions by system organ class and preferred term – EPIK-P1 (Full study population)

Adverse reactions	Pediatric Patients N = 39		Adult Patients N = 18		All Patients N = 57	
	Grades 1 to 4 %	Grade 3-4 %	Grades 1 to 4 %	Grade 3-4 %	Grades 1 to 4 %	Grade 3-4 %
Gastrointestinal disorders						
Diarrhea	13%	0%	22%	0%	16%	0%
Stomatitis[1]	15%	0%	17%	0%	16%	0%
Nausea	2.6%	0%	6%	0%	3.5%	0%
Vomiting	2.6%	0%	6%	0%	3.5%	0%
General disorders and administration site conditions						
Mucosal dryness[2]	2.6%	0%	6%	0%	3.5%	0%
Metabolism and nutrition disorders						
Hyperglycemia	5%	0%	28%	0%	12%	0%
Dehydration	2.6%	0%	6%	6%[4]	3.5%	1.8%[4]
Decreased appetite	0%	0%	6%	0%	1.8%	0%
Nervous system disorders						
Headache	0%	0%	17%	0%	5%	0%
Skin and subcutaneous tissue disorders						
Dry skin	2.6%	0%	17%	0%	7%	0%
Alopecia	0%	0%	17%	0%	5%	0%
Acne[3]	0%	0%	6%	0%	1.8%	0%

Grading according to CTCAE Version 4.03.

[1]Stomatitis: including stomatitis and aphthous ulcer. Mouth ulceration has been reported in PROS patients treated with alpelisib under compassionate use programs outside of EPIK-P1.

[2]Mucosal dryness: including dry mouth and vulvovaginal dryness.

[3]Dermatitis acneiform has been reported in PROS patients treated with alpelisib under compassionate use programs outside of EPIK-P1.

[4]No Grade 4 adverse reactions were reported. Source: [PROS CO-Appendix 2-Table 17.3-1.2]

Table 36: Selected Laboratory Abnormalities Occurring in study EPIK-P1 (Full study population)

Laboratory Abnormality	Pediatric Patients N = 39		Adult Patients N = 18		All Patients N = 57	
	Grades 1 to 4%	Grade 3-4 %	Grades 1 to 4%	Grade 3-4%	Grades 1 to 4 %	Grade 3-4%
Biochemical parameters						
Decreased phosphate	64%	0%	56%	11%[3]	61%	3.5%[3]
Decreased calcium (corrected)	59%	0%	67%	0%	61%	0%
Increased creatinine	46%	0%	11%	0%	35%	0%
Increased glycosylated hemoglobin (HbA1c) [1]	28%[1]	N/A[1]	67%[1]	N/A[1]	40%[1]	N/A[1]
Increased glucose[2]	10%	0%	11%	6%[3]	11%	1.8%[3]

Abbreviation: N/A, not available.
[1] No CTCAE grade available. All laboratory abnormalities with an incidence ≥ 5.7% are shown, regardless of value at baseline.
[2]Glucose increase is an expected laboratory abnormality of PI3K inhibition.
[3] No Grade 4 laboratory abnormalities were reported.
Source: [PROS CO-Appendix 2-17.2-5.4] [PROS CO-Appendix 2-17.3-1.6]

The Applicant's Position:

All preferred terms in the clinical trial database of EPIK-P1 were considered adverse reaction candidates and screened based on incidence rates for all AEs, SAEs, AEs leading to hospitalization, AEs leading to dose interruption, AEs leading to dose reduction, fatal AEs, AEs determined to be related to alpelisib as per physician assessment, AEs occurring within 14 days of treatment initiation, time to onset of first AE. All adverse reaction candidates have undergone medical review on a case-by-case basis to determine if they should be added to the adverse reactions list, taking into consideration the current knowledge of alpelisib safety profile (including adverse reactions mentioned in the Piqray USPI). The Novartis Global Safety Database has been used as an additional source of data supporting the medical review, as it contains safety reports from patients receiving alpelisib for PROS indications within the MAP/ATU programs (including within and outside EPIK-P1).

Laboratory abnormalities were screened from shift tables of parameters worsening during treatment with alpelisib and medically reviewed on a case-by-case basis to identify any trend or pattern (e.g. sustained post-index changes with no apparent alternative explanations) and

determine if they should be included in the table of laboratory abnormalities. As with adverse reactions, the current knowledge of alpelisib safety profile (including laboratory abnormalities mentioned in the Piqray USPI) and information from the Novartis Global Safety Database were used to support the medical review.

The frequencies of selected adverse reactions and laboratory abnormalities were calculated using the clinical database from EPIK-P1, considering on-treatment events only. Physician's assessment of study drug relationship was not utilized for frequency calculation.

There were no hematological laboratory abnormalities identified (Table 36).

The FDA's Assessment:

As noted in section 8.1.1, the treatment plan for patients enrolled in the expanded access program included a recommended visit schedule that required adverse events to be collected at every visit. The treatment plan also provided recommendations for safety monitoring that included chemistry and hematology laboratory studies. Ultimately, treating physicians determined the frequency of patient visits and the safety assessments obtained according to local practice. Although the safety data reported in EPIK-P1 were not collected on a set schedule as typically done in a clinical trial, based on the data submitted in this NDA and the known safety profile of alpelisib in the oncology setting, the data were considered adequate for assessment in this rare patient population.

The Applicant employed a conservative approach to collection of adverse event data. If the event start date was completely or partially missing, the event was considered to have started during the study period (i.e., during the treatment phase), unless there was an associated end date prior to alpelisib initiation. Based on these imputation rules, some adverse events with a partial start date collected (e.g., year documented, but no month or date) were classified as treatment-emergent adverse events (TEAEs). Additionally, if the event start and end dates were completely or partially missing with no specification of whether the event is ongoing, then the event was assumed to occur during the study period. If the start date was completely missing but the end date was not missing or partially missing then the event was assigned to the study period if the end date was in the study period, or it was assigned to the pre-index period if the end date was before the index date.

See Table 37 and Table 38 for the FDA's analysis of treatment-emergent adverse reactions by system organ class (SOC) and laboratory abnormalities worsening from baseline. The majority (82%) of patients in EPIK-P1 experienced at least one treatment-emergent adverse event (TEAE). The most common (≥10%) all-grade TEAEs were diarrhea, stomatitis, and hyperglycemia. Adverse events of Grade 3 or 4 severity were generally rare. There were no new safety signals identified. Furthermore, despite the limitations of the small sample size, there were no significant adverse events and no consistent pattern of adverse events by SOC that were detected more frequently in pediatric patients than in adult patients.

As mentioned by the Applicant, many adverse events may be related to the patient's PROS diagnosis or reflect a complication of the patient's underlying disease. Based upon the mechanism of action and known safety profile of alpelisib, and review of narratives for supplemental information, the FDA considered the toxicities listed in Table 37 to be treatment-emergent adverse reactions observed in EPIK-P1. Reported adverse events that were considered to be clearly related to pre-existing medical conditions or manifestations of PROS based on data provided and thus not considered adverse reactions were "disseminated intravascular coagulation", "vascular malformations", "inflammation" and "gait disturbance". Events of "hypoglycemia" and "pain in extremity" were considered on a case-by-case basis to determine whether they constituted adverse reactions and were each reported in 3.5% of patients. Additionally, clinically relevant adverse reactions in <5% of patients in EPIK-P1 included nausea, vomiting, dehydration and mucosal dryness.

Table 37: Treatment-emergent Adverse Reactions (≥5%) in EPIK-P1

Adverse Reaction	All Patients N = 57 N (%)	
	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders		
Diarrhea	16	0
Stomatitis[a]	16	0
Metabolism and nutrition disorders		
Hyperglycemia	12	0
Skin and subcutaneous tissue disorders		
Eczema	7	0
Dry skin	5	0
Alopecia	5	0
Nervous system disorders		
Headache	5	0
Infections and infestations		
Cellulitis	5	1.8

Source: ADSL (Subject-Level Analysis Dataset) - 2021-07-28, ADAE (Adverse Events Analysis Data) - 2021-07-28.
Variables used: USUBJID, AGEGR2, FSPFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER
Grading according to CTCAE Version 4.03.
[a]Stomatitis: including stomatitis and aphthous ulcer.

[b]Mucosal dryness: including dry mouth and vulvovaginal dryness.

Regarding laboratory abnormalities (Table 38), the FDA's analysis is based on the number of patients with a baseline value and at least one post-treatment value. The FDA agrees with the Applicant's position that the worst post-index biochemistry and hematological abnormalities were mostly Grade 1 or Grade 2. The FDA does not assign attribution to laboratory abnormalities to determine whether they are related to the study treatment).

Table 38: Laboratory Abnormalities Worsening from Baseline in ≥10% of Patients in EPIK-P1

Laboratory Abnormality	**All Patients**[a] N = 57 N (%)	
	All Grades (%)	**Grade 3 or 4** (%)
Chemistry		
Decreased calcium (corrected)	60	0
Decreased phosphate	59	5
Increased glucose	56	11[b]
Increased glycosylated hemoglobin (HbA1c)[d]	38[d]	N/A[d]
Increased creatinine	31	0
Increased bilirubin	29	2[b]
Increased potassium	24	0
Increased triglycerides	19	0
Decreased magnesium	18	0
Increased aspartate aminotransferase	17	0
Increased cholesterol	13	0
Decreased albumin	13	0
Decreased sodium	12	2[b]
Decreased potassium	12	0
Increased gamma glutamyl transferase	11	0
Increased alanine aminotransferase	10	0
Hematology		
Decreased leukocytes	22	0

Laboratory Abnormality	All Patients[a] N = 57 N (%)	
	All Grades (%)	Grade 3 or 4 (%)
Decreased hemoglobin	20	6
Decreased lymphocytes	20	0
Decreased neutrophils	19	0
Increased lymphocytes	17	0
Decreased platelets	14	2[b]

Source: ADSL (Subject-Level Analysis Dataset) - 2021-07-28, ADLB (Laboratory Analysis Data) - 2021-07-28.
Variables used: USUBJID, AGEGR2, FSPFL, PARAM, ABLFL, AVAL, ANRLO, ANRHI, ONTRTFL, TRTEDT, ADT, TRTSDT, ADY, ATOXGRN

Grading according to CTCAE Version 4.03.
Abbreviation: N/A, not available.
[a]The denominator used to calculate the rate varied from 9 to 50 based on the number of patients with a baseline value and at least one post-treatment value.
[b]No Grade 4 laboratory abnormalities were reported.
[c]Glucose increase is an expected laboratory abnormality of PI3K inhibition.
[d]No CTCAE grade available. For HbA1c, baseline values increasing post-treatment to a value above the upper limit of the normal range (≥5.7%) are considered increased.

Vital Signs

Data:

Table 39: Notable vital sign values during the study period in pediatric (< 18 years) and adult (≥ 18 years patients) (Full study population)

Vital sign	Category	Pediatric patients N=39 n/m (%)	Adult patients N=18 n/m (%)
Number of patients with any vital sign		36	18
Systolic blood pressure	High	17/35 (48.6)	0/17 (0.0)
	Low	3/35 (8.6)	0/17 (0.0)
Diastolic blood pressure	High	12/35 (34.3)	2/17 (11.8)
	Low	2/35 (5.7)	0/17 (0.0)
Pulse rate	High	15/34 (44.1)	1/17 (5.9)
	Low	10/34 (29.4)	0/17 (0.0)
Weight	High	0/29 (0.0)	0/15 (0.0)

Vital sign	Category	Pediatric patients N=39 n/m (%)	Adult patients N=18 n/m (%)
	Low	1/29 (3.4)	6/15 (40.0)

Number (N) represents total number of patients included in the analysis. Numbers (m) represents counts of patients with vital signs data. Numbers (n) represent counts of patients in each category.

Low/High: Indicating abnormal value/change from index date.

Systolic blood pressure [mmHg] High: ≥ 95th percentile of the age and height group and Low: ≤ 5th percentile of the age and height group. Diastolic blood pressure [mmHg] High: >= 95th percentile of the age and height group and Low: ≤ 5th percentile of the age and height group.

The Applicant's Position:

No clinically meaningful trends were noted in vital signs results among pediatric as well as adult patients (Table 39). All the abnormalities were transient and none of them were considered clinically significant by the investigator as they normalized without medical intervention.

The FDA's Assessment:

Based on the limited data provided in the application, the FDA cannot make conclusive determinations regarding the impact of alpelisib on vital signs of patients with PROS. Additionally, as noted by the Applicant in the Clinical Overview of the NDA, elevations in vital signs of blood pressure and pulse rate in pediatric patients were evaluated as isolated events, preceded and followed by normal readings, and likely due to the general phenomenon of agitation when visiting a healthcare provider, as communicated by the provider.

Electrocardiograms (ECGs)

Data:

All patients (N=57): During the study period, electrocardiogram (ECG) assessments were available for only 6/57 patients (10.5%). 2/5 patients (40%) reported with a QTcF > 450 ms to ≤ 480 ms.

Pediatric patients (N=39): During the study period, ECG assessment was available for only 3/39 pediatric patients (7.7%). 1/3 patients (33.3%) reported with a QTcF >450 ms to ≤ 480 ms.

Adult patients (N=18): During the study period, ECG assessment was available for only 3/18 adult patients (16.7%). 1/2 patients (50%) reported with a QTcF >450 ms to ≤ 480 ms [PROS EPIK-P1-CSR-Table 14.3-7.2].

The Applicant's Position:

No evidence of clinically significant increased risk of QT prolongation was observed with alpelisib at doses between 50 mg and 250 mg, and none of the patients reported a QTcF that was > 480 ms based on a limited number of patients with available ECG data.

The FDA's Assessment:

Based on the limited ECG data in EPIK-P1, the FDA cannot make definitive assessments regarding QTc prolongation observed with alpelisib administration in patients with PROS. The multidisciplinary review for PIQRAY (NDA 212526) describes the potential for QT/QTc prolongation. Section 6.3 states that an analysis of clinical ECG data demonstrated the absence of large effect (i.e. >20 ms) on QTcF prolongation at the recommended 300 mg dose with or without fulvestrant. Further, the review states that preclinical studies indicate a minimal risk of an electrophysiological effect with alpelisib. The recommended dose of alpelisib in the PIQRAY label exceeds the recommended dose for adult patients based on EPIK-P1 in the VIJOICE label. Therefore, the review team considers the risk of QTcF prolongation to be minimal and does not recommend inclusion of QTcF prolongation as a risk in product labeling. Refer to the PIQRAY label and multidisciplinary review for further information.

Safety results of supportive studies: Study X2101 and Study X1101

Beyond the EPIK-PI study, the safety analyses focused on 167 adult patients receiving alpelisib monotherapy at higher dose in Studies X2101 and X1101 (details of the study design are provided in Table 9 in Section 7.1); results from these respective datasets were consistent with those reported from EPIK-P1 for adult patients (Of note, the details of the safety data from these 2 studies were previously provided to the FDA within the Piqray NDA). 167 patients were exposed to single-agent alpelisib in the dose-finding Studies X2101 and X1101 in adult patients with solid tumors (oncology setting). Details of the safety data from these 2 studies were previously provided to the FDA within the Piqray NDA.

Overall, the review of safety data in PROS patients in the context of EPIK-P1 and of the ongoing compassionate use programs has not identified any unexpected safety concern. The safety profile of alpelisib in this population (starting dose with food of 250 mg in adults and 50 mg in pediatrics) is consistent with the known mechanism of action and compares favorably to the known safety profile previously characterized in adult patients in the oncology setting. Overall, the incidence and severity of AEs were lower in EPIK-P1 compared to the oncology setting, especially in pediatric patients. Data from EPIK-P1 support a favorable and manageable safety profile of alpelisib in patients with PROS.

The FDA's Assessment:

The FDA agrees with the Applicant's comments pertaining to the supportive safety analyses of 167 adult patients with advanced solid tumors harboring PIK3CA gene alteration who received alpelisib as a single agent in Studies X2101 and X1101.

8.2.5. **Analysis of Submission-Specific Safety Issues**

Data:

Table 40: Overview of adverse events of special interest by preferred term and age category (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (<18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Safety topic PT	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
GI toxicity (Nausea Vomiting Diarrhea) (AESI)	2 (18.2)	0	3 (25.0)	0	2 (12.5)	0	7 (17.9)	0	6 (33.3)	0	13 (22.8)	0
Diarrhoea	1 (9.1)	0	3 (25.0)	0	1 (6.3)	0	5 (12.8)	0	4 (22.2)	0	9 (15.8)	0
Nausea	0	0	0	0	1 (6.3)	0	1 (2.6)	0	1 (5.6)	0	2 (3.5)	0
Vomiting	0	0	1 (8.3)	0	0	0	1 (2.6)	0	1 (5.6)	0	2 (3.5)	0
Abdominal pain	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Constipation	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Gastroenteritis	1 (9.1)	0	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Hyperglycaemia (AESI)	0	0	1 (8.3)	0	2 (12.5)	0	3 (7.7)	0	5 (27.8)	0	8 (14.0)	0
Hyperglycaemia	0	0	0	0	2 (12.5)	0	2 (5.1)	0	5 (27.8)	0	7 (12.3)	0
Ketosis	0	0	1 (8.3)	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Type 2 diabetes mellitus	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Hypersensitivity (AESI)	0	0	0	0	1 (6.3)	0	1 (2.6)	0	4 (22.2)	0	5 (8.8)	0
Eczema	0	0	0	0	1 (6.3)	0	1 (2.6)	0	3 (16.7)	0	4 (7.0)	0
Angioedema	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Vaginal ulceration	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Stomatitis (AESI)	2 (18.2)	0	3 (25.0)	0	1 (6.3)	0	6 (15.4)	0	3 (16.7)	0	9 (15.8)	0
Aphthous ulcer	1 (9.1)	0	1 (8.3)	0	1 (6.3)	0	3 (7.7)	0	3 (16.7)	0	6 (10.5)	0

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (<18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Safety topic PT	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Stomatitis	1 (9.1)	0	2 (16.7)	0	0	0	3 (7.7)	0	0	0	3 (5.3)	0

A patient with multiple severity grades for an AE is only counted under the maximum grade.
AEs for which there is a specific clinical interest for the indication in connection with alpelisib treatment.
Adverse evets reported are intended as treatment emergent events.
MedDRA version 24.0, CTCAE version 4.03, Case Retrieval Strategy version released 05MAY2021.
Source: EPIK-P1-CSR-Table 14.3.1-2.1

The Applicant's Position:
AESIs are groupings of AEs that were selected during clinical development based on medical significance, the mechanism of action of alpelisib coupled with biological plausibility, as well as nonclinical and clinical observations. The AESIs selected for alpelisib in PROS are GI toxicity (nausea, vomiting, and diarrhea), hyperglycemia, hypersensitivity, severe cutaneous reactions, rash, pneumonitis, pancreatitis, and stomatitis. Note that in the table above, pneumonitis, severe cutaneous reactions and pancreatitis are not listed as there were no patients in EPIK-P1 with these AESIs (Table 40).

8.2.5.1 GI toxicity: nausea, vomiting, and diarrhea

Data and The Applicant's Position:
Gastrointestinal AESIs (nausea, vomiting, diarrhea) were of low grade (grade 1 or 2) in all patients; no grade 3/4 AEs were reported. In pediatric patients, SAEs and AEs leading to dose interruption (vomiting) occurred in one patient. In adult patients, no SAEs were reported, and two AEs led to dose interruption (vomiting and nausea in one patient each) [PROS EPIK-P1-CSR-Table 14.3.1-3.3].

8.2.5.2 Hyperglycemia

Data and The Applicant's Position:
Hyperglycemia AESIs were of low grade (grade 1 or 2) in all patients. No grade 3/4 AEs were reported. A single SAE in an adult patient was reported. There were no AEs leading to dose interruption in all patients [PROS EPIK-P1-CSR-Table 14.3.1-3.2].

8.2.5.3 Hypersensitivity

Data and The Applicant's Position

Hypersensitivity AESIs were of low grade (grade 1 or 2) in all patients (Table 40). No grade 3/4 AEs were reported. A single AE of grade 1 vaginal ulceration was considered to be treatment-related, although this patient had a relevant history of uterine ulceration (grade 2). The event of grade 1 angioedema was reported as related to ramipril by the Investigator, and the event resolved with no action taken with alpelisib.

8.2.5.4 Stomatitis

Data and The Applicant's Position

Stomatitis AESIs were of low grade (grade 1 or 2) in all patients (Table 40). No grade 3/4 AEs were reported. Most of these AEs were manageable with appropriate concomitant medication and no action was taken with alpelisib.

8.2.5.5 Severe cutaneous reactions

No cases of severe cutaneous reactions AESI have been reported in EPIK-P1.

8.2.5.6 Rash

No cases of rash AESI has been reported in EPIK-P1. However, in the compassionate use programs outside of EPIK-P1, rash AESI and pruritus have been reported in 11 and 3 PROS patients, respectively. A causal relationship with alpelisib was suspected in the majority of patients. Considering that skin reactions such as rash and pruritus are a class-effect of PI3K/mTOR inhibitors and have been commonly observed with alpelisib in the oncology setting, these terms are proposed for inclusion in the PROS USPI as events reported in compassionate use programs outside of EPIK-P1.

8.2.5.7 Pneumonitis

No cases of pneumonitis AESI has been reported in EPIK-P1.

8.2.5.8 Pancreatitis

No cases of pancreatitis AESI, including no increases in lipase or amylase, have been reported in EPIK-P1.

The FDA's Assessment:

The FDA agrees with the Applicant's description of AESIs in EPIK-P1. Although there were no cases of rash, pneumonitis or pancreatitis occurring in EPIK-P1, the USPI for VIJOICE contains instructions for dosage modifications and relevant information in the *Warnings and Precautions* section based on the observation of these toxicities in the clinical experience of alpelisib in the oncology setting (refer to PIQRAY label for additional details).

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data and The Applicant's Position:
No patient-reported outcomes were collected and analyzed in EPIK-P1.

The FDA's Assessment:
Refer to the FDA's comments in section 8.1.2 (*Study Results*) under subheading "Efficacy Results – Secondary or exploratory COA (PRO) endpoints."

8.2.7. Safety Analyses by Demographic Subgroups

Data and The Applicant's Position:

Age

The safety data in pediatric (<18 years) and adult (≥ 18 years) patients are described in Section 8.1.3. The incidence and severity of treatment-emergent AEs is low in pediatric patients (compared to the adult population), which is likely to reflect the lower doses used in this population compared to the adult patients (with PROS as well as in the oncology setting). Overall, in view of the established clinical benefit in patients with PROS, alpelisib is characterized by an acceptable and manageable safety profile in pediatric patients of ≥ 2 years of age with PROS.

Race

Data on race was available from very few patients (7 out of 57 patients). Therefore, no subgroup analysis was performed based on race.

The FDA's Assessment:
In general, the incidence and severity of treatment-emergent adverse events were low in both pediatric and adult patients. The FDA agrees that alpelisib appears to have a manageable safety profile in patients with PROS, including children and adolescents; however, due to the small sample size, the retrospective nature of data collection and the single-arm design of EPIK-P1, additional information including long-term data is needed to draw definitive conclusions. The FDA has issued a postmarketing requirement to conduct comprehensive safety analyses from clinical studies to further characterize the potential serious risk of long-term adverse effects of alpelisib on growth and development in pediatric patients.

In addition, the FDA agrees that the limited data on race and ethnicity collected in EPIK-P1 precludes a subgroup analysis based on this demographic factor. Race and ethnicity data were reported in few patients in this study as the majority of patients were treated in France, where local regulations restrict the collection of such data. The FDA has issued a postmarketing requirement to conduct a multiregional clinical trial to verify and describe the clinical benefit of

alpelisib in a study population that is sufficiently reflective of the U.S. patient population to support generalizability of results to U.S. patients with PROS.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Not applicable.

The FDA's Assessment:
The FDA has no comments.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
Data and The Applicant's Position:
A carcinogenicity study is currently ongoing in line with previously correspondence with the FDA. Novartis anticipates that the final report will be submitted to the FDA in 2024.

The FDA's Assessment:
The FDA agrees; see Section 13 regarding requested PMRs.

Human Reproduction and Pregnancy
Data and The Applicant's Position:
There was no exposure of alpelisib in pregnant and lactating women in EPIK-P1. Based on animal data and on the known mechanism of action, alpelisib can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to conclude on the drug-associated risk. Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus.

The FDA's Assessment:
The FDA agrees. The product labeling includes a warning for embryo-fetal toxicity and appropriate guidance on contraception.

Pediatrics and Assessment of Effects on Growth
Data and The Applicant's Position:
No impact on the growth and pubertal development of pediatric patients was observed in the PROS settings. However, a conclusive determination on the risk cannot be made due to the limited number of PROS patients with growth and development data.

The FDA's Assessment:
The data submitted in the application pertaining to growth and development of pediatric patients with PROS were significantly limited by the small sample size (n=39) and missing data

due to non-systematic collection of key parameters (e.g., height, weight, pubertal development). Therefore, the FDA is unable to determine whether alpelisib has an adverse impact on growth and development in pediatric patients with PROS. The FDA has issued a postmarketing requirement to conduct safety analyses from clinical studies that further characterize the potential serious risk of long-term adverse effects of alpelisib on growth and development, including an assessment of growth plate abnormalities and development of teeth in a sufficient number of pediatric patients. The PMR requires patients to be monitored for growth and development using age-appropriate screening tools, and to be evaluated for growth as measured by height, weight, heigh velocity and heigh standard deviation scores, age at adrenarche if applicable, age at menarche if applicable (females) and Tanner stage.

Additionally, as indicated in the label, based on animal toxicity data in which rats administered alpelisib exhibited growth plate thickening and bone/joint defects, regular monitoring of growth and development in pediatric patients treated with alpelisib is recommended.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data and The Applicant's Position:

Overdose: There is limited experience of overdose with alpelisib in clinical studies: in the oncology setting, alpelisib was administered at doses up to 450 mg once daily in fed condition. There are few reports of alpelisib accidental overdose as per the search conducted in the Novartis Global Safety Database using MedDRA (version 24.0) and presented in Periodic Safety Update Reports (PSURs). Overall, a review of the reports of overdose did not reveal any pattern or new safety information relevant to the benefit-risk assessment for alpelisib.

Drug abuse potential: There is no data to indicate drug abuse potential with alpelisib **(**PSUR covering period from 24-Nov-2020 to 23-May-2021).

Withdrawal and rebound: In clinical studies with alpelisib for treatment of advanced solid tumors, patients were followed for 28/30 days or longer after discontinuation of alpelisib, and no withdrawal or rebound effects were observed. No studies have been conducted to assess withdrawal and rebound effects from alpelisib treatment as a single agent for PROS. In the mouse model recapitulating the human CLOVES disease (PROS), withdrawal of alpelisib led to the recurrence of lesions and the development of asymmetric extremity hypertrophy within four weeks (Venot et al 2018). Only five patients discontinued from EPIK-P1 and no data regarding the rebound effect was reported within 30 days post treatment discontinuation.

The FDA's Assessment:

The FDA agrees with the summary above.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data and The Applicant's Position:
Hyperglycemic hyperosmolar nonketotic syndrome (HHNKS), a serious metabolic complication associated with hyperglycemia, and Drug reaction with eosinophilia and systemic symptoms (DRESS), a severe cutaneous adverse reaction, have been identified during post-marketing surveillance in oncology patients. Data from the post-marketing experience with alpelisib in the oncology setting and from the literature have not shown evidence of other unexpected or new safety information that could be attributable to treatment with alpelisib, thus supporting the safety profile of alpelisib as currently known.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

Data and The Applicant's Position:
Substantial post-marketing experience with alpelisib is already available, as the product is approved for the treatment of select patients with advanced or metastatic breast cancer in > 60 countries worldwide. The safety data are reviewed on an ongoing basis and presented in PSURs (altogether, the PSURs submitted to the FDA cover the period from 24-May-2019 to 23-May-2021). No unexpected safety concerns have been observed from the analysis of specific safety topics, including off-Label use, or in specific subpopulations including elderly patients.
The safety of alpelisib administered to PROS patients in ongoing compassionate use programs was reviewed in the PSURs and no new safety concerns were identified in PROS patients. Safety in long-term use is considered missing information in both pediatric and adult patients. In order to monitor the safety profile during long-term use of alpelisib and identify any new safety issues that may arise, data in patients receiving alpelisib treatment for more than 5 years will be evaluated in the Phase 2 studies EPIK-P2 and EPIK-P3.

The FDA's Assessment:
The FDA agrees with the Applicant's position. Additionally, the FDA has issued a postmarketing requirement to conduct comprehensive safety analyses from clinical studies that further characterize the potential serious risk of long-term adverse effects of alpelisib on growth and development in pediatric patients.

8.2.11. Integrated Assessment of Safety

Data and The Applicant's Position:

The safety profile of alpelisib in EPIK-P1 study (starting dose with food of 250 mg in adults and 50 mg in pediatrics) in patients with PROS is consistent with the mechanism of action of alpelisib and compares favorably to the known safety profile characterized in adult patients in the oncology setting. No unexpected safety concerns have been identified in the PROS population in EPIK-P1, which included 57 patients (39 pediatric patients from 2 to 17 years of age and 18 adult patient) with respect to the product safety profile established in more than 5,292 patients and with a cumulative post-marketing exposure of ~3374 patient-treatment years. Notably, the incidence and severity of treatment-emergent AEs is low in EPIK-P1, especially in pediatric patients, which is likely to reflect the lower dose used in this population compared to approved indication in oncology setting.

No life-threatening treatment related events, no AEs leading to discontinuation, and no deaths were observed. There were no unique toxicities noted in the pediatric population.

EPIK-P1 data further support the fact that the observed safety risks are predominantly of mild/moderate severity, can be managed with appropriate supportive therapy, alpelisib dose interruptions, and/or dose modifications and that the overall safety profile is favorable in both adult and pediatric patients with PROS. No patient discontinued due to an AE, and most of them were still on treatment at the time of the data cut-off date. The safety profile remained consistent and manageable irrespective of the patient's duration of treatment (i.e., 6 months, 12 months, etc.).

Although the laboratory tests were taken according to local practice and less frequently than expected in a prospective study assessing the safety of alpelisib, there was no major issue detected. Overall, the routine clinical and laboratory evaluations performed were adequate to assess the safety of alpelisib. The hematological or clinical chemistry abnormalities observed were mostly grade 1 and grade 2, with no apparent trend in the majority of cases, and could often be attributed to the underlying or concurrent medical conditions. The vital sign abnormalities were transient and none of them were considered clinically significant.

Based on the mechanism of action and available clinical experience, the main expected toxicities of alpelisib were GI toxicities (mainly diarrhea, but also nausea and vomiting), hyperglycemia, stomatitis, hypersensitivity and skin toxicities (mainly rash). In addition, pneumonitis is a class effect with PI3K/mTOR inhibition. However, no cases of rash and pneumonitis were reported in EPIK-P1. All cases of GI toxicities (22.8%), stomatitis (15.8%), hyperglycemia (14.0%), and hypersensitivity (8.8%) were of low grade and manageable and controlled with appropriate monitoring (FPG and HbA1c in case of hyperglycemia), supportive therapies, and/or standard medical care as clinically indicated, and are considered reversible upon dose reduction and/or temporary dose interruption.

In conclusion, alpelisib has a manageable safety profile for the treatment of PROS in adult and pediatric patients aged 2 years and older. In both pediatric and adult patients with PROS, the safety profile is consistent with the mechanism of action of alpelisib and compares favorably to the known safety profile characterized in adult patients in the oncology setting.

The FDA's Assessment:

The FDA concurs with the Applicant's description of the observed safety profile of alpelisib in patients with PROS. Review of data collected in EPIK-P1 has not led to the identification of new safety signals nor a trend of increased toxicity in either the pediatric or adult patient populations. In general, the incidence of adverse events was low regardless of patient age. The product labeling will include description of the severe adverse reactions observed in the oncology population and included as Warnings in section 5 of the PIQRAY label, which may not have been observed in EPIK-P1 given the relatively small sample size. The most common (≥10%) treatment-emergent adverse events in the safety population were diarrhea, stomatitis and hyperglycemia, and were largely considered manageable. Given the predominance of low severity (Grade 1 or Grade 2) adverse events and the prolonged duration of exposure observed (approximately 33% of patients received alpelisib for at least two years), long-term administration of alpelisib in this population appears feasible and reasonably safe. Additional data from EPIK-P2 will be submitted as part of a post-marketing requirement and will provide further information on the long-term safety profile in patients with PROS. Overall, the safety profile of alpelisib is acceptable when assessed in the context of a severe and potentially life-threatening disease, and in the context of the lack of FDA-approved therapies for PROS.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

EPIK-P1 was designed as a single-arm clinical study in patients who were treated as part of an expanded access program for alpelisib. The data included in the protocol and statistical analysis plan for EPIK-P1 was abstracted from medical charts of eligible patients with PROS treated with alpelisib at participating clinical sites . All eligible patients who received alpelisib were considered for the primary analysis population; however, 20 patients were excluded due to lack of imaging assessments at baseline. Those patients who were excluded due to lack of imaging assessments or site agreement may have different prognostic characteristics than those included in the analysis population who did have imaging assessments; this type of selection bias could potentially result in issues of internal validity for the estimate of response rate. This may also potentiate concerns of external validity, as the patients with imaging assessments at baseline and meeting the other eligibility criteria may not reflect the overall population of patients with PROS. However, this concern of generalizability does not invalidate the estimation of treatment effect for EPIK-P1 demonstrated by response data, but instead indicates a need

for caution in the interpretation and application of these results to a wider population.

Additional potential sources of bias for the EPIK-P1 study include measurement or investigator bias. The patients on the MAP as well as the investigators were not blinded to the receipt of alpelisib treatment, which may influence investigator assessment of whether alpelisib improved their patient's clinical condition. Similarly, there could be differences in clinical monitoring by physician or clinical site. To reduce this bias in the estimation of treatment effect, a blinded independent central review (BICR) was implemented for radiologic assessment of lesion imaging to inform the primary endpoint of overall response. By using a blinded and independent review of radiologic imaging, FDA considers this concern of investigator bias to be sufficiently mitigated.

An additional measurement bias may be caused by the choice of time window for the assessment of the primary endpoint of response rate. Given that there was not pre-specified schedule or frequency of lesion assessments, the chosen window for the establishment of a baseline scan or the window of assessment of response rate at 24 weeks will impact both the number of patients eligible for the analysis population as well as those for whom lesion response can be assessed. For EPIK-P1, the chosen window for baseline scans is 24 weeks prior to first dose of alpelisib and for response rate assessment is 4 weeks before or after the 24 week landmark time for response. The Applicant provided sensitivity analyses with modified windows of assessment, which result in slightly different response rates indicating these study design choices may have an impact on the observed results; though it is noteworthy that small sample sizes for these analyses and overlapping 95% confidence intervals reduce the inference that can be derived from the results. In addition, the choices for the assessment windows for baseline scan and for response rate at 24 weeks were discussed with FDA during the development of the EPIK-P1 protocol, and were considered reasonable given the limited available data.

Given the retrospective nature of the data collection from the patients in the MAP, careful evaluation of the data to ensure data quality and reduce bias, especially related to measurement, was necessary. EPIK-P1 implemented several quality control measures taken throughout the development and implementation of eCRF, data collection, cleaning, and analysis. These measures including utilizing an experienced contract research organization for data management and standardized data abstraction, collection of the electronic case report form using an EDC platform (compliant with 21 CFR Part 11) with a predefined protocol and statistical analysis plan, and data validation checks at point of data entry. Lastly, the inspection of the Office of Scientific Integrity found no major issues with respect to the data for the efficacy analysis (see Section 4.1). Overall, FDA considered the data of sufficient quality to support the assessment of efficacy and safety from EPIK-P1.

Overall, there are other minor statistical concerns in EPIK-P1 that may impact or bias study results. First, the selection of the patient population using local assessment of the PIK3CA

mutation. In general, to ensure reliability of patient selection across sites, a central testing approach may be employed, but given the large number of patients from a single site in this study, we can expect some consistency in the testing approach. Also, given the limited sample size and retrospective nature of data collection, important predictive or prognostic characteristics may not be adequately captured. It is noteworthy that since this study is not comparative, confounding of the treatment effect by these factors is not a major concern, but the characterization of response rate in subgroups may be affected by these limited data. However, response is notably an objective endpoint as the disease is not likely to spontaneously regress. Lastly, most of the data comes from a single clinical site. This lack of diversity in the patient data may reduce the ability to interpret the results to the broader population of PROS patients. While these concerns are important to consider in the interpretation of the EPIK-P1 results, these statistical issues are unlikely to materially impact the overall conclusion that the observed treatment effect of alpelisib on the endpoints of response rate and DOR is reasonably likely to predict clinical benefit in patients with severe PROS.

There were no formal sample size calculations for EPIK-P1, and no hypothesis testing was performed. The response rate was summarized using summary statistics (frequency counts and percentages) along with 2-sided 95% CIs using the Clopper-Pearson exact method. The precision of the estimate for different values of the response rate was evaluated via the width of the 95% confidence interval. The point estimate for RR observed in the EPIK-P1 trial (27%) is not precise given the small sample size, as illustrated by the wide 95% CI of 14-44%. Additionally, the estimation of the treatment effect of alpelisib among subgroups within the spectrum of patients with PROS was also limited due to the small sample size. However, given the rarity and severity of the disease, the lack of available therapy, and results that provide compelling evidence of durable reduction in the size of PROS lesions with an endpoint responsibly likely to predict clinical benefit, the evidence is deemed appropriate for accelerated approval. Additional data from a larger, prospective, randomized trial evaluating response rate and duration of response among key patient subgroups (e.g. by age, PROS subtype and type of PIK3CA mutation) will occur as part of the post-marketing clinical trial.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the evaluation of clinical data from EPIK-P1, the review team recommends accelerated approval of alpelisib under the provisions of 21 CFR 314.510 Subpart H for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy. The FDA's recommendation is based on the favorable benefit:risk assessment for alpelisib based on review of data from EPIK-P1, a single-arm clinical study of patients with severe or life-threatening PROS who were enrolled in an expanded access program to receive alpelisib for compassionate use.

PROS is a very rare collection of clinical entities that result from somatic gain-of-function alterations in the PIK3CA gene. There is significant variability in the genotypes and phenotypes observed in affected patients; however, the hallmarks of PROS include sporadic and mosaic overgrowths (manifesting either as a spectrum or isolated features) that are congenital or noted in early childhood. There are limited management options with no FDA-approved treatments for PROS, and PROS does not spontaneously regress.

The FDA considered the expanded access program data source of EPIK-P1 to be acceptable and appropriate given the rarity of PROS (estimated to have a prevalence of less than 5,000 patients in the US) and its high unmet medical need. Additionally, although the majority of patients enrolled in EPIK-P1 were treated outside of the US, based on the treatment landscape for PROS and the lack of locoregional disease variability (no known differences in PROS biology or epidemiology), the results are applicable to the intended population in the US.

The FDA considers response rate with supportive DOR to be endpoints that are reasonably likely to predict clinical benefit in patients with severe manifestation of PROS who require systemic treatment for their disease. The observed response rate of 27% (95% CI: 14, 44) determined by blinded independent central review and the durability of responses, including 60% of patients with a response lasting at least one year, observed in EPIK-P1 coupled with the known safety profile are supportive of accelerated approval.

Although all radiologic responders in EPIK-P1 had PIK3CA mutations categorized as “frequent” and had the CLOVES subtype of PROS, volumetric reduction in the sum of target lesion(s) not meeting the 20% threshold for confirmed radiologic response was observed in 8 of the 16 patients with the non-CLOVES subtype and/or a “less frequent” PIK3CA mutation in the efficacy population (of note, BICR assessment was not reported for 4 of the 16 patients due to lack of imaging of the target lesion at Week 24 and these patients were therefore categorized as nonresponders). It is also important to note that interpretation of subgroup analyses of response rate by PROS subtype are hampered by the small sample size of the EPIK-P1 efficacy population overall, and the even smaller sizes of each subgroup. The review team therefore considered it appropriate to grant accelerated approval to alpelisib to patients with severe manifestations of PROS regardless of subtype or mutation type.

In order to obtain the information needed to verify the clinical benefit of alpelisib in patients with PROS who will likely require chronic treatment, a PMR study will be conducted to provide longitudinal data in additional patients to better characterize the duration of response. Clinical outcome assessment data will also be systematically collected to confirm clinical benefit. Additionally, the study required under the PMR will enroll patients across a large number of clinical sites internationally in order to ensure that alpelisib is studied in an appropriately diverse patient population with respect to race, ethnicity, mutation type, PROS subtype, and age; this

will enable better characterization of the treatment effect across the spectrum of patients with PROS.

The safety findings in EPIK-P1 are consistent with the known safety profile of alpelisib observed in the oncology setting. There were no new safety signal identified, and the incidence and severity of treatment-emergent adverse events were low in both pediatric and adult patients. Overall, alpelisib appears to have a manageable safety profile in patients with PROS; however, due to the small sample size and retrospective nature of data collection, additional information including long-term data on growth and development in pediatric patients is needed and will be provided as a postmarketing requirement. Additional safety data from EPIK-P3 will also be submitted as a post-marketing requirement to further characterize the safety profile, including known serious risks of alpelisib, in patients with PROS.

In conclusion, the benefit:risk assessment for alpelisib is favorable, and the FDA recommends accelerated approval of alpelisib for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy.

X X

Xiaoxue Li, PhD
Primary Statistical Reviewer

Pallavi Mishra-Kalyani, PhD
Statistical Team Leader

X X

Sonia Singh, MD
Primary Clinical Reviewer

Diana Bradford, MD
Clinical Team Leader

9 Pediatrics

The Applicant's Position:

The safety and effectiveness of alpelisib have been established in pediatric patients with PROS 2 to 17 years. Treatment of these patients with alpelisib is supported by evidence from a retrospective chart review study (EPIK-P1) in 39 pediatric patients: 11 patients aged 2 to 5 years, 12 patients aged 6 to 11 years, and 16 patients aged 12 to 17 years.

Details of efficacy in pediatric patients are described under 'Subgroup analysis of primary endpoint' in the sections above (Section 8.1.2). Also, details of safety results in pediatric patients are described in the above sections (Section 8.2.4).

The safety and effectiveness of alpelisib in pediatric patients below the age of 2 years have not been established.

The FDA's Assessment:

The FDA agrees with the description provided by the Applicant. Refer to Section 13 regarding the need for a PMR to further characterize the safety of alpelisib in pediatric and adolescent patients. Alpelisib was granted Orphan Drug Designation for the treatment of PROS (DRU-2019-7108) on November 18, 2019; the application is therefore exempt from the requirements of the Pediatric Research Equity Act.

10 Labeling Recommendations

Data and The Applicant's Position:
The FDA approved label for Piqray (alpelisib) served as the basis for the proposed Vijoice label. Information specific to patients with PROS (primarily based on data from EPIK-P1) was added throughout the label. Information specific to patients with breast cancer which was not deemed relevant for the PROS indication was deleted. Text from the Piqray label that was deemed relevant to the PROS indication was retained throughout the proposed Vijoice label. Carton and container labeling specific to Vijoice was also submitted.

The FDA's Assessment: FDA revised the labeling in accordance with 21 CFR Chapter 1 Subchapter C Part 201 Subparts A and B, guidances and current labeling practices.

1 INDICATIONS AND USAGE

- FDA refined the indication statement to specify that VIJOICE is for the treatment of patients with "severe manifestations" of PIK3CA-Related Overgrowth Spectrum (PROS).
- Indication statement was also revised to specify that VIJOICE is indicated for patients who require systemic therapy.

2 DOSAGE AND ADMINISTRATION

- Dosage instructions and modifications for toxicity were edited for clarity and completeness to ensure safe dosage for adult and pediatric patients.

5 WARNINGS AND PRECAUTIONS

- Due to the small number of patients in the EPIK-P1 study, this section relies heavily on the clinical experience from PIQRAY for the treatment of breast cancer.
- To specify that VIJOICE is not for the treatment of oncology patients, the following text was included, "VIJOICE is not approved for use in the oncology setting."

6 ADVERSE REACTIONS

- (b) (4) Due to the small number of patients in the safety population and because there were no major discrepancies observed in the incidence or severity of adverse reactions between adults and pediatric patients, the FDA revised the adverse reactions table to reflect the entire study population.

6.2 Postmarketing

(b) (4) The FDA decided to omit this information because it is not relevant to the indicated population for VIJOICE.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- Information specifying human equivalent dosing relative to dosages used in animal studies was added to inform providers about embryo-fetal risks with the use VIJOICE in pregnant patients.

8.4 Pediatric Use

- FDA included a statement that there is insufficient data to determine whether VIJOICE has an adverse impact on growth and recommends monitoring of growth and development during treatment with VIJOICE.

8.5 Geriatric Use

- FDA deleted text regarding geriatric use of PIQRAY because there were no geriatric patients treated with VIJOICE.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

- FDA included a description of impairment of fertility observed in animal studies.

14 CLINICAL STUDIES

- (b) (4) Due to the small number of patients, FDA revised the presentation of efficacy data to reflect the entire efficacy population, and notes that there were no major discrepancies in efficacy between adults and pediatric patients.
- The FDA also revised the description and presentation of efficacy data to include only confirmed responses, as this was considered the relevant regulatory endpoint.

17 PATIENT COUNSELING

- FDA included a recommendation to counsel patients that VIJOICE can cause alopecia.
- Instructions on how to create an oral suspension for patients who cannot swallow pills were removed from this section because the description for patients and their caregivers is presented in the Patient Information document.

11 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The risks of alpelisib are acceptable in the indicated patient population with a serious and potentially life-threatening condition; the safe use of alpelisib can be adequately implemented in the postmarketing setting through instructions contained in product labeling and routine pharmacovigilance. A post-marketing requirement to further evaluate the safety profile in pediatric and adolescent patients will be included in the approval letter. No additional risk management strategies are recommended.

12 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication. The application was discussed at the Medical Policy and Program Review Council during the review period.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

Five PMRs and two PMCs were deemed necessary to ensure the safe and effective use of alpelisib for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS. The following post-marketing requirements/commitments, reviewed and agreed to by the Applicant, will be included in the action letter for this NDA:

FDA PMR #1:

Conduct a multiregional clinical trial to verify and describe the clinical benefit of alpelisib, through more precise estimation of confirmed objective response rate and mature response duration per blinded independent review, in adult and pediatric patients 2 years of age and older with PIK3CA-Related Overgrowth Spectrum (PROS), including those with severe manifestations of PROS. Responding patients will be followed for at least 36 months from the onset of response, or until disease progression, whichever comes first. Evaluate a sufficient number of patients to characterize response rate and durability of response by PIK3CA mutation type (frequent hotspot mutations vs. other less frequent mutations), PROS subtype, and age (2 – 5 years, 6 – 11 years, 12 – 17 years, ≥ 18 years). Include patient narratives and additional outcomes measures (such as clinical outcomes assessments) to support the assessment of clinical benefit in the study report. The distribution of race and ethnicity in the patient population studied should be sufficiently reflective of the U.S. patient population to support generalizability of results to U.S. patients with PROS.

Milestones:

Draft Protocol Submission:	07/2022
Final Protocol and Analysis Plan Submission:	10/2022
Trial Completion:	02/2027
Final Report Submission:	08/2027

FDA PMR #2:

Conduct comprehensive safety analyses from clinical studies that further characterize the potential serious risk of long-term adverse effects of alpelisib on growth and development, including an assessment of growth plate abnormalities and development of teeth in a sufficient number of pediatric patients. Monitor patients for growth and development using age-appropriate screening tools. Include evaluations of growth as measured by height, weight, height velocity and height standard deviation scores, age at adrenarche if applicable, age at menarche if applicable (females) and Tanner stage. Monitor patients until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

Milestones:

Final Protocol Submission (Analysis Plan):	05/2023
Study Completion:	03/2030
Final Report Submission:	09/2030

FDA PMR #3:

Conduct comprehensive safety analyses from ongoing trials to further assess the serious risks of alpelisib, including severe hypersensitivity, severe cutaneous adverse reactions and pneumonitis, in patients with PROS over a sufficient period of follow-up time to characterize these risks. The analysis should include appropriate monitoring and risk mitigation strategies.

Final Protocol Submission (Analysis Plan):	05/2023
Study Completion:	03/2030
Final Report Submission:	09/2030

FDA PMR#4

Conduct a carcinogenicity study in rats to evaluate the potential for carcinogenicity. A carcinogenicity protocol for a Special Protocol Assessment (SPA) was submitted and reviewed by the FDA prior to initiating the study

Milestones:

Final Protocol Submission:	04/2022
Study Completion:	06/2023
Final Report Submission:	05/2024

FDA PMR #5:

Conduct a carcinogenicity study in mice to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

Milestones:

Draft Protocol Submission:	05/2025
Final Protocol Submission:	09/2025
Study Completion:	08/2026
Final Report Submission:	07/2027

FDA PMC #1:

Conduct a study using a higher starting dose of alpelisib (i.e., 125 mg) in addition to the 50 mg once daily starting dose in pediatric patients 6 to 17 years of age to evaluate the pharmacokinetics, safety, and clinical outcomes (including confirmed objective response rate and duration of response) for dose optimization in this patient population.

Milestones:

Draft Protocol Submission:	07/2022
Final Protocol Submission:	10/2022
Study Completion:	02/2027
Final Report Submission:	08/2027

FDA PMC#2:

Conduct an analysis from EPIK-P3, an ongoing single-arm study, to further describe the long-term outcomes of patients receiving alpelisib for the treatment of severe manifestations of PROS. Evaluate a sufficient number of patients over a sufficient period of time to better characterize clinical response over time, and include case narratives describing additional patient outcome measures (such as clinical outcomes assessments) to support assessment of benefit of alpelisib in this patient population.

Milestones:

Interim Report Submission	09/2026
Study Completion:	03 /2028
Final Report Submission:	09 /2028

14 Division Director (DHOT) (NME ONLY)

X

John K. Leighton, PhD

15 Division Director (OCP)

X

Nam Atiqur Rahman, PhD

16 Division Director (OB)

X

Yuan-Li Shen, PhD

17 Deputy Division Director (Clinical)

X

Martha Donoghue, MD

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Julia Beaver, MD

19 Appendices

19.1. References

The Applicant's References:

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The FDA's References:

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19.2. Financial Disclosure

The Applicant's Position:
Financial disclosure information was provided for all clinical investigators involved in EPIK-P1, the single covered clinical study. There was one investigator with disclosable financial arrangements. Novartis does not have concerns regarding the overall integrity of the data from EPIK-P1.

The FDA's Assessment:

In accordance with the Code of Federal Regulations (CFR) Title 21, Part 54, the Applicant submitted a financial disclosure certification document (FDA Form 3454) in Module 1.3.4. The document includes a list of all principal investigators, including sub-investigators, who participated in EPIK-P1. According to the Applicant, 100% of the clinical investigators submitted financial disclosure forms. No clinical investigators are full or part-time employees of the Applicant; however, disclosable financial arrangements and interests were identified for (b) (6) (b) (6) The Applicant has submitted an FDA Form 3455 (b) (6) disclosing (b) (6) proprietary interest (b) (6) (b) (6)

In his Investigator Financial Interests and Disclosure Statement Form, (b) (6) indicates that neither he, his spouse or any dependent children: have entered into a financial arrangement with the Study Sponsor(s)/Co-Development Partner(s) whereby the value of the compensation could be influenced by the outcome of the trial, such as a bonus, royalty or other financial incentive (i.e., compensation that could be higher for a favorable outcome than for an unfavorable outcome); hold any significant equity interest in the Study Sponsor(s)/Co-Development Partner(s) (stock, stock options, or other financial interests) that exceeds $50,000.00 US dollars; received significant payments of other sorts having total value in excess of $25, 000.00 from Study Sponsor(s)/Co-Development Partner(s) other than payments for conducting on this clinical study or other clinical studies. Additionally, in this form, (b) (6) (b) (6)

In Module 1.3.4, the Applicant highlights the following to support the claim that any potential bias was minimized:

- All data included in EPIK-P1 from (b) (6) site were collected (b) (6) (b) (6).
- The Applicant entered into contractual agreements with (b) (6) site on

July 20, 2020, and with (b) (6) on July 29, 2020, after the cut-off date (March 9, 2020) had been applied for EPIK-P1.

- EPIK-P1 used a blinded independent review committee to select target lesions and assess both target and non-target lesion response throughout study treatment (local assessment of lesion was not collected and not part of the application).
- The Applicant's data management team and a designated CRO ensured database quality processes were followed and implemented a monitoring plan to comply with standard operating procedures (for further details, see the section "Compliance with Good Clinical Practices" above).
- Several investigators across multiple sites/countries contributed to EPIK-P1.

(b) (6) site was the largest enroller, accounting for 44 of the 57 patients in the safety population and 28 of 37 patients in the efficacy subset. In FDA's assessment, the steps taken to minimize bias of clinical trial results, in particular the use of BIRC for assessment of the primary and key secondary endpoints of radiologic response rate and duration of response, by any of the disclosed arrangements or interests were sufficient.

(b) (6) site accounted for 8 of the 10 confirmed responders in the EPIK-P1 efficacy population. On-site inspection found no regulatory violations. See Section 4.1 "Office of Scientific Investigations (OSI)" for further information.

The remaining 2 confirmed responders in EPIK-P1 were enrolled at another site (b) (6) (b) (6) and at a site in the US (b) (6). Additionally, two unconfirmed responders were enrolled at (b) (6). Notably, the proportion of patients who were confirmed responders at (b) (6) site (29%) is fairly similar to the proportion of patients who were confirmed responders at other sites (22%) and to the response rate overall (27%).

Covered Clinical Study (Name and/or Number): Retrospective chart review study of patients with PIK3CA-Related Overgrowth Spectrum (PROS) who have received alpelisib as part of a compassionate use program (EPIK-P1)/BYL719F12002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): One		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: One Significant equity interest held by investigator in study: None Sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Data and The Applicant's Position:
The details of nonclinical pharmacology and toxicology are provided above in Section 5.

The FDA's Assessment:
Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

The Applicant's Position:
No Population PK analysis was performed in EPIK-P1.

19.4.1.1. Executive Summary

The FDA's Assessment:

Not applicable.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

No Population PK analysis was performed in EPIK-P1.

The FDA's Assessment:
Not applicable.

19.4.1.3 PPK Review Issues

The Applicant's Position:
Not applicable.

19.4.1.4 Reviewer's Independent Analysis

The Applicant's Position:
Not applicable.

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:
Not applicable.

19.4.2.2. ER (efficacy) assessment Summary

The Applicant's Position:

No ER (efficacy) analysis was performed in EPIK-P1.

The FDA's Assessment:
Not applicable.

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:
Not applicable.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:

No ER (efficacy) analysis was performed in EPIK-P1.

19.4.2.5. ER review issues

The Applicant's Position:

Not applicable

19.4.2.6. Review's Independent Analysis

The Applicant's Position:
Not applicable

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

No ER (efficacy and safety) analysis was performed in EPIK-P1.

The FDA's Assessment:
Not applicable.

19.4.3. Data Supporting Response to Alpelisib against Less Frequent PIK3CA Mutations

The FDA's Assessment:

In response to an FDA information request (February 02,2022), the Applicant provided the following nonclinical data to support the inhibitory activity of alpelisib against less frequent PIK3CA mutations:

Fritsch et al., 2014

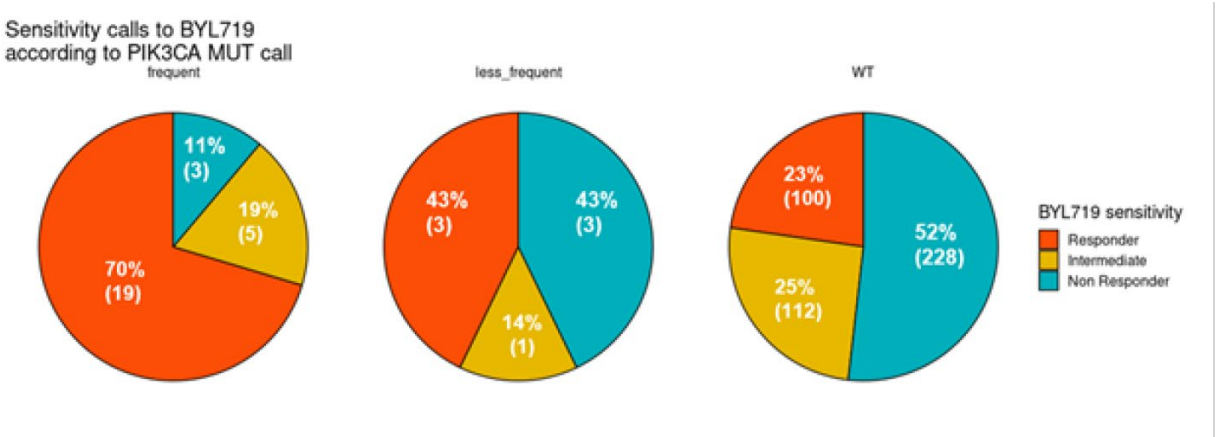
- Alpelisib was tested against 442 kinases, at a concentration of 10 µmol/L, including PIK3CA with frequent (C420R, E542K, E545K, and H1047L) and less frequent (H1047Y, I800L, M1043I, and Q546R) mutations. All 8 PIK3CA mutants were found to be inhibited to a similar extent by alpelisib, with IC50s in the range of 4.0-4.8 nmol/L.

- The anti-tumor effect of alpelisib was assessed in 9 distinct cancer patient-derived xenograft (PDX) models carrying PIK3CA genetic alterations, including PIK3CA frequent (H1047R, E545K and C420R) and less frequent (M1043I and Q546K) mutations. Efficacy was reported as the percentage change in tumor volume on the last day of treatment relative to start of treatment (Day 0) with alpelisib at 50 mg/kg/day for 14 to 16 days. Eight of 9 PDX models that carried a mutation and/or amplification in PIK3CA (including less frequent mutants) responded to alpelisib.

In addition, internally available cancer cell line and cancer PDX models were analyzed by the Applicant using the categorization of frequent and less frequent mutants as in the EPIK-P1 CSR. Published data were re-annotated using the PIK3CA mutation frequency call and the sensitivity read out were compared in the various groups. Any amino acid change that was not previously reported was labelled as less frequent. For these analyses, PIK3CA mutation status, as well as sensitivity metrics measured for alpelisib, were used as previously reported in the publications as follows: Cancer cell lines: Fritsch et al., 2014; PDX models: Gao et al., 2015.

- The association to alpelisib sensitivity was tested by comparing the responder to the non-responder cell line populations using a Fisher test (using wild-type (WT) as reference). The population of responder cell lines was enriched in PIK3CA frequent mutant lines compared to the non-responder population. As shown in Figure 11, the responder rate in the frequent mutation population was higher (70%) than in the less frequent mutation (43%) or the WT population (23%). Of note, the number of observations within the less frequent category was lower (n=7) compared with the frequent (n=27) and the WT (n=440) categories.

Figure 11: Sensitivity calls to alpelisib (NVP-BYL719) according to PIK3CA mutation calls (Frequent, Less Frequent and WT)

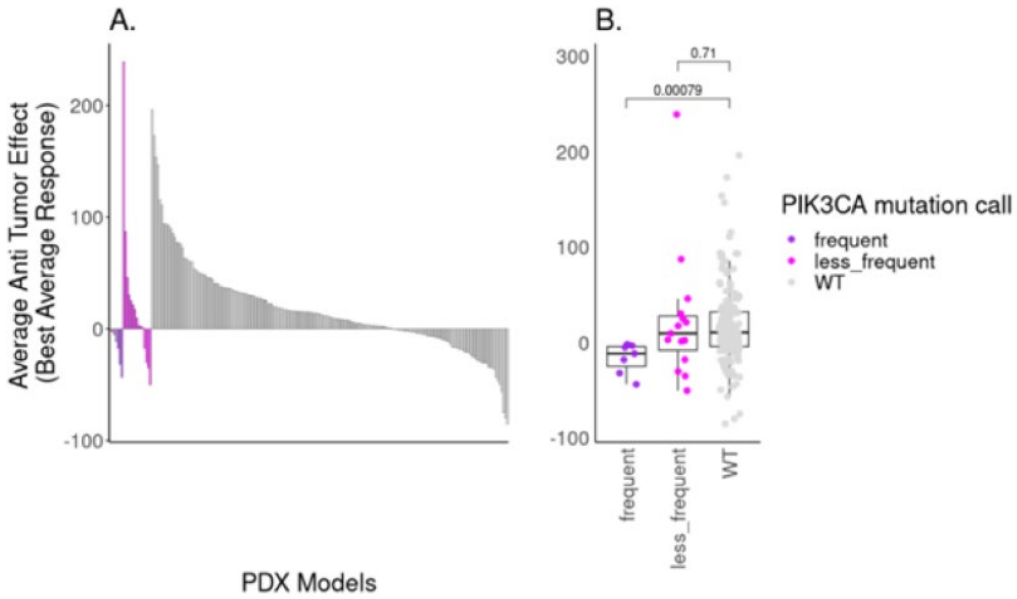


Source: Applicant's figure based on Fritsch et al., 2014. Alpelisib (NVP-BYL719) sensitivity profile separated according to PIK3CA mutational status (frequent, less frequent, WT (wild type). The response rate is reported as %

with number of cell lines into brackets. Cell lines with EC50 ≤ 3.04 mmol/L and Amax ≤ 30% were responders, cell lines with higher values for both cutoffs were non-responders, and cell lines that did not meet these criteria were intermediate. Response to FDA information request (February 02, 2022).

- As re-analyzed by the Applicant, a significant difference of anti-tumoral response in PDX models (N=210, across cancer indications) was observed in the frequent mutation population (n=7) as compared with the WT. In contrast, with the less frequent population as compared with the WT, no significant difference in anti-tumoral response was observed (Figure 12).

Figure 12: Evaluation of best average response to alpelisib (NVP-BYL719) in a panel of cancer Patient-derived xenograft models



Source: Applicant's figure based on Gao et al, 2015. ***Panel A:*** *Waterfall plot of Best Average response to alpelisib across all PDX models (all indications – n=210).* ***Panel B.*** *Boxplot of same response categorized by PIK3CA mutation status and mutation category – Reported p-value from test used to compare the means of response to alpelisib in the two mutation categories as compared to WT population. WT (wild type). Response to FDA information request (February 02, 2022).*

In response to an FDA information request (February 17,2022), the following published literature supporting alpelisib activity against less frequent PIK3CA mutations was provided:

<u>Morin et al., 2022</u>
After 12 months of follow-up, alpelisib treatment was associated with improvement in signs and symptoms, morphological lesions and vascular anomalies in the two infants with PIK3CA-related overgrowth spectrum with PIK3CA less frequent mutations (N1044K mutation and a deletion).

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